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UNITED STATES BANKRUPTCY COURT
SOUTHERN DISTRICT OF NEW YORK

In re:	:	Chapter 11
PURDUE PHARMA L.P., *et al*.,	:	Case No. 19-23649 (RDD)
Debtors.[1]	:	(Jointly Administered)

NAS AD HOC COMMITTEE'S LIMITED OBJECTION TO DISCLOSURE STATEMENT AND SOLICITATION PROCEDURES MOTION

The NAS Children Ad Hoc Committee ("**NAS Ad Hoc**"), through its counsel, Tarter Krinsky & Drogin LLP, respectfully submits this objection (the "**Objection**") to the (i) Debtors' *First Amended Disclosure Statement for Chapter 11 Plan for Purdue Pharma L.P. and its Affiliated Debtors* [Docket No. 2734] (the "**Disclosure Statement**") for the *First Amended Joint Chapter 11*

[1] The Debtors in these cases, along with the last four digits of each Debtor's registration number in the applicable jurisdiction, are as follows: Purdue Pharma L.P. (7484), Purdue Pharma Inc. (7486), Purdue Transdermal Technologies L.P. (1868), Purdue Pharma Manufacturing L.P. (3821), Purdue Pharmaceuticals L.P. (0034), Imbrium Therapeutics L.P. (8810), Adlon Therapeutics L.P. (6745), Greenfield BioVentures L.P. (6150), Seven Seas Hill Corp. (4591), Ophir Green Corp. (4594), Purdue Pharma of Puerto Rico (3925), Avrio Health L.P. (4140), Purdue Pharmaceutical Products L.P. (3902), Purdue Neuroscience Company (4712), Nayatt Cove Lifescience Inc. (7805), Button Land L.P. (7502), Rhodes Associates L.P. (N/A), Paul Land Inc. (7425), Quidnick Land L.P. (7584), Rhodes Pharmaceuticals L.P. (6166), Rhodes Technologies (7143), UDF L.P. (0495), SVC Pharma L.P. (5717) and SVC Pharma Inc. (4014). The Debtors shall include their affiliates and other entities under their control. The Debtors' corporate headquarters is located at One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901.

Plan of Reorganization of Purdue Pharma L.P. and its Affiliated Debtors [Docket No. 2731] (the "**Plan**")[2] and (ii) *Debtors' Motion to Approve (I) the Adequacy of Information in the Disclosure Statement, (II) Solicitation and Voting Procedures, (III) Forms of Ballots, Notices, and Notice Procedures in Connection Therewith, and (IV) Certain Dates With Respect Thereto*, (the "**Solicitation Procedures Motion**") [Docket No. 2489]. For its Objection, the NAS Ad Hoc respectfully submits the *Declaration of Scott R. Bickford in Support of NAS Ad Hoc Committee's Limited Objection to Disclosure Statement and Solicitation Procedures Motion* (the "**Bickford Declaration**"), attached hereto as Exhibit 1, and respectfully states as follows:

PRELIMINARY STATEMENT

1. The Disclosure Statement, including the personal injury trust distribution procedures (the "**PI TDP**") (drafted without the input of the NAS Ad Hoc[3]), filed less than 3 days before the deadline to object to the Disclosure Statement as Exhibit C to the *Plan Supplement Pursuant to the First Amended Joint Chapter 11 Plan of Reorganization of Purdue Pharma, L.P. and its Affiliated Debtors* [Docket No. 2732], fails to identify the eligibility or qualifications for any NAS Child to obtain a distribution on account of a filed proof of claim. This failure to disclose is particularly devastating to the NAS Children because, under the PI TDP, it appears the NAS Children, despite the thousands of claims filed on their behalf, will very likely receive ***no distribution*** under the Plan.[4] In fact, based on the NAS Ad Hoc's analysis of the PI TDP, the NAS

[2] Capitalized terms used but not defined herein shall have the meaning given to such term in the Disclosure Statement or Plan, as the case may be.

[3] Pursuant to the Order Appointing Mediators [Docket No. 895] (the "**Mediation Order**"), the NAS Ad Hoc participated in the Court ordered mediation for the NAS Monitoring Trust Documents. The NAS Ad Hoc sought, but was denied, participation with respect to the PI Trust Documents.

[4] While the NAS Ad Hoc received a version of the PI TDP prior its filing, the NAS Ad Hoc has not had ample opportunity to conduct a detailed review of the PI TDP. In any event, it appears to be substantially similar to prior circulated versions of the PI TDP, none of which provide fair or adequate relief for the NAS Children. Because NAS Ad Hoc received the PI TDP only a few days before the deadline to file this Objection, it reserves the right to supplement this Objection after it has had an opportunity to fully review the PI TDP.

Children will receive only *0.7% in the aggregate* of the $750 million to be distributed to adult personal injury claimants under the Plan. The Plan is therefore, at its core, inconsistent with the Court's admonition that: "the parties simply need to conclude these negotiations so that a plan can be filed because, as we all know, every day that passes some poor soul is not getting either the counseling that he or she needs, or an NAS baby is no longer a baby, and her grandparents are not getting the help they need." See In re Purdue Pharma, L.P., Case No. 19-23649(RDD) (Bankr. S.D.N.Y.), Dec. 15, 2020 Hr'g. Tr., at 36:6-11 (Judge Drain comments). Unfortunately, the Disclosure Statement fails to disclose the Plan fails to provide the NAS Children or their caregivers with the help they need.

2. Next, the Solicitation Procedures Motion does not provide a mechanism for voting the Class 9 NAS Monitoring Claims. Because the beneficiaries of this class are a class of claimants, as opposed to individual claimants, the equivalent of a class representative needs to be appointed to vote the claims in Class 9. A similar solution was utilized in In re Insys Therapeutics, Inc., et al., Case No 19-11292 (Bankr. D. Del.).

3. In addition, the Plan as currently constituted is patently unconfirmable, as it: (i) unfairly prejudices and improperly classifies the NAS Children; (ii) contains unconstitutional releases; and (iii) contains a non-consensual channeling injunction. The NAS Children should be separately classified under section 1122(a) of the Bankruptcy Code from all other unsecured claims because their injuries, in contrast to the injuries alleged by adults who claim addiction to opioids, are: (a) the result of involuntary in utero exposure to opioids; and (b) more severe and permanent, certainly with respect to impacts upon structural brain development.

4. Further, the claims of NAS Children have a higher value because they generally are not subject to the constraints of statutes of limitation or contributory-comparative negligence

defenses that are applicable to adult personal injury claimants. Moreover, a cursory review of the PI TDP shows that it unfairly prejudices the NAS Children, as it appears to (i) arbitrarily and artificially (a) require proof of a temporal relationship between the prescription of certain NDC-labeled Purdue opioids and the victim's first documented instance of addiction or substance abuse and (b) tie recovery to the direct and persistent use of a Purdue product, which is unique to individuals in that no other class of creditor, public or private, is compelled to prove that its harm resulted from a Purdue product and (ii) treat the NAS Children substantially different than other claimants within the personal injury Claimant Class, which violates Section 1123(a)(4) of the Bankruptcy Code. A plan that does not satisfy sections 1122 and 1123 of the Bankruptcy Code cannot satisfy the requirements of section 1129 of the Bankruptcy Code and therefore should not be distributed to creditors as it is patently unconfirmable.

5. Similarly, to the extent the release and channeling injunction provisions purport to release the claims of "any Cause of Action held by a natural person who is not yet born or who has not yet attained majority as of the Petition Date or as of the Effective Date," the same are unconstitutional. The Due Process Clause of the U.S. Constitution and numerous state constitutions prohibit such a release.

6. Lastly, the extraordinarily broad release provisions, which discharge from liability the Debtors' officers, directors, employees, etc., the non-Debtor affiliates, and anyone remotely connected to the foregoing, do not satisfy the standards set forth in Metromedia for a third-party release.

BACKGROUND

7. The NAS Ad Hoc represents the legal interests of thousands of children injured by fetal exposure to synthetic opioids listed on the Debtor's Proof of Claim. As addressed herein, in

many instances the guardians are individuals other than the birth mother, a fact which presents unique difficulty to NAS Children in meeting certain requirements of the PI TDP.

8. Often, the harm which opioids have caused to a NAS Child manifests shortly after birth in a neonatal intensive care unit ("**NICU**"). Among other problems, NAS Children experience tremors, seizures, mottling, skin excoriation, regurgitation, agitation, pain, tachypnea, hyperactive reflexes, excessive yawning, stuffiness, vomiting, inability to sleep, high pitched crying, excessive runny nose, diarrhea, inability to thrive, weight loss, prematurity, hydrocephalus, heavy sweating, inability to suck, and low birth weight.[5]

9. Damages to the NAS Children reach far beyond the weeks spent withdrawing from opioids. Statistically significant numbers of these children are born with latent heart defects, spina bifida, and congenital malformations like cleft palate, club foot, and anklioglossia (tongue-tie), all requiring painful and expensive surgeries.

10. Beyond the NICU, NAS Children may be subject to a statistically significant risk of developmental delays that can ruin the rest of their lives. The complications that NAS Children experience can include.

a. 1st Year – Growth retardation and psychomotor developmental delays.[6]

b. One Year Old – Deficits in locomotor, personal/social, hearing and speech, hand/eye coordination and intellectual performance.[7]

c. Two to Three Years Old – Deficits in motor, expressive language and receptive language.[8]

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[5] See *Declaration of Dr. Kanwaljeet S. Anand* (attached as Exhibit B to the Bickford Declaration) at ¶4.

[6] McGlone L, Mactier H. Infants of opioid-dependent mothers: neurodevelopment at six months. Early Hum Dev2015;91:19-21.

[7] Hans SL, Jeremy RJ. Postneonatal mental and motor development of infants exposed in utero to opioid drugs. Infant Mental Health J 2001;22:300-15.

[8] Conradt E, Flannery T, Aschner JL, et al. Prenatal Opioid Exposure: Neurodevelopmental Consequences and Future Research Priorities. Pediatrics 2019;144.Exhibit 1- Anand at ¶10.

d. After Three Years Old – In addition, NAS Children can experience deficits in personality structure and functioning: decreased sense of well-being, responsibility, self-control, psychological mindedness, empathy and social maturity.[9]

e. Four to Five Years Old – Decreased language comprehension and expression.[10]

f. Five to Twelve Years Old – Deficits in verbal, performance, externalizing and internalizing problems.[11]

g. Late Childhood – IQ impairment, lower language abilities in exposed children, higher rates of behavioral problems that become worse with time.[12]

11. In addition to the above, a significant number of NAS Children experience latent effects and damages, which may include: heart defects, brain damage, learning disabilities, behavioral and emotional disorders, attention deficit hyperactivity disorder, cognitive impairment, deficits in independent functioning, depression and anxiety disorders, and autism spectrum disorders.[13]

12. The legal representatives which comprise the NAS Ad Hoc and their associates are responsible for filing 87 actions on behalf of NAS Children, including class actions which seek medical surveillance filed in 34 states. Given the foregoing, the recovery of reasonable and necessary costs associated with damages and lifelong care needs of the NAS Children place this unique group of claimants at the top of the list of creditors. In fact, the aggregate value of the

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[9] Konijnenberg C, Sarfi M, Melinder A. Mother-child interaction and cognitive development in children prenatally exposed to methadone or buprenorphine. Early Hum Dev 2016;101:91-7.

[10] Fill MA, Miller AM, Wilkinson RH, et al. Educational Disabilities Among Children Born With Neonatal Abstinence Syndrome. Pediatrics 2018;142:pii: e20180562.

[11] Id.

[12] Id.; Bauman PS, Levine SA. The development of children of drug addicts. Int J Addict 1986;21:849-63.

[13] Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:314 e1-11; Dawson AL, Razzaghi H, Arth A, et al. Maternal exposures in the National Birth Defects Prevention Study: Time trends of selected exposures. Birth Defects Res A Clin Mol Teratol 2015;103:703-12; Lind JN, Interrante JD, Ailes EC, et al. Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review. Pediatrics 2017;139.

claims of NAS Children may very well exceed the real value of the claims of all other categories of personal injury claimants in the Debtors' cases.

13. The NAS Ad Hoc has been monitoring and participating in this case from the outset. Beyond typical informal comments, mediation, and other negotiations with the Debtors and other parties in interest, the NAS Ad Hoc filed the following documents:

a. *Conditional Consent with Reservation of Rights of the NAS Children AD HOC Committee to Motion of Debtors for Entry of Order (i) Establishing Deadlines for Filing Proofs of Claim and Procedures Relating Thereto, (ii) Approving Proof of Claim Forms and (iii) Approving the Form and Manner Thereof* [Docket No. 754] (the "**Bar Date Reservation of Rights**"), reserving its rights with respect to the Debtors' bar date motion;

b. *Motion For Entry of An Order Pursuant To Fed. R. Bankr. P. 9014 And 7023 Permitting Them To File A Class Proof of Claim And Granting Related Relief* [Docket No. 1362] (the "**NAS Class Motion**"), seeking to permit the NAS Ad Hoc to file a class proof of claim;

c. *Motion for Entry of Order Pursuant to 11 U.S.C. §§ 105(a) and 107(b) and Fed. R. Bankr. P. 9018 Authorizing the Filing of Certain Information and Exhibits Under Seal in Connection with the NAS Children Ad Hoc Committee's Ex Parte Motion Requesting a Court Order Authorizing Examinations Pursuant to Federal Rules of Bankruptcy Procedure 2004 and 9006* [Docket No. 2139], seeking to file a redacted 2004 motion (the "2004 Motion");

d. *Motion for Entry of Order Pursuant to 11 U.S.C. §§ 105(a) and 107(b) and Fed. R. Bankr. P. 9018 Authorizing the Filing of Certain Information and Exhibits Under Seal in Connection with the NAS Children Ad Hoc Committee's Ex Parte Motion Requesting a Court Order Authorizing Examinations Pursuant to Federal Rules of Bankruptcy Procedure 2004 and 9006* [Docket No. 2340], seeking to file redacted exhibits related to the 2004 motion; and

e. *Motion to Authorize the NAS Children Ad Hoc Committee's Motion Entry of Order Pursuant to 11 U.S.C. Sections 105(a) and 107(b) and Fed. R. Bankr. P. 9018 Authorizing the Filing of Certain Information and Exhibits Under Seal in Connection with the Reply and Supplemental Declaration* [Docket No. 2538] (the "2004 Reply"), seeking to file a reply and supplemental declaration under seal in connection with the NAS Ad Hoc's 2004 motion.

14. The NAS Ad Hoc first raised due process concerns in connection with the establishment of a deadline to file claims. See Bar Date Reservation of Rights (noting that

constructive notice was likely insufficient to provide unknown creditors the proper due process). Those concerns remain given the extraordinarily broad releases sought by the Debtors in the Plan. See generally, Plan at § 10.6-10.9.

15. Further, the PI TDP manipulates traditional tort recoveries available to NAS Children and would thereby set an unfairly high bar for recovery by the NAS Children, as opposed to the very low bar for recovery which the PI TDP sets for the adult personal injury claimants. The NAS Ad Hoc has sought extensive discovery from the Debtors and their non-Debtor affiliates, the Sacklers and the so-called IACs in its efforts to meet this high bar. See 2004 Reply. To date, it has received some, but not all of the information it requested.

I. The Disclosure Statement Fails to Provide Creditors with "Adequate Information," as Required by Section 1125 of the Bankruptcy Code, by Failing to Disclose the Impact of the PI TDP on the NAS Children

16. Section 1125 of the Bankruptcy Code provides that a disclosure statement must contain "adequate information" describing a confirmable plan. 11 U.S.C. § 1125. The Bankruptcy Code defines "adequate information" as: "[i]nformation of a kind, and in sufficient detail…that would enable such a hypothetical reasonable investor of the relevant class to make an informed judgment about the plan…" 11 U.S.C. § 1125(a)(1). Indeed, Congress intended the disclosure statement "to be the primary source of information upon which creditors and shareholders could rely in making an informed judgment about a plan of reorganization." In re Scioto Valley Mortg. Co., 88 B.R. 168, 170 (Bankr. S.D. Ohio 1988); see also Momentum Mfg. Corp. v. Employee Creditors Comm. (In re Momentum Mfg. Corp.), 25 F.3d 1132, 1136 (2d Cir. 1994) ("The Code obliges a Debtor to engage in full and fair disclosure"); In re Adelphia Commc'ns Corp., 352 B.R. 592, 596 (Bankr. S.D.N.Y. 2006) (The Bankruptcy Code "provides that acceptances or rejections

of a reorganization plan can't be solicited without first giving the creditors or others so solicited a court approved disclosure statement, which provides 'adequate information.'").

17. To be approved, a disclosure statement must include sufficient information to apprise creditors of the risks and financial consequences of the proposed plan. See In re McLean Indus., Inc., 87 B.R. 830, 834 (Bankr. S.D.N.Y. 1987) ("[S]ubstantial financial information with respect to the ramifications of any proposed plan will have to be provided to, and digested by, the creditors and other parties in interest in order to arrive at an informed decision concerning the acceptance or rejection of a proposed plan").

18. Although the adequacy of the disclosure is determined on a case-by-case basis, the disclosure must "contain simple and clear language delineating the consequences of the proposed plan on [creditors'] claims and the possible [Bankruptcy] Code alternatives…" In re Copy Crafters Quickprint, Inc., 92 B.R. 973, 981 (Bankr. N.D.N.Y. 1988). Section 1125 of the Bankruptcy Code is biased towards more disclosure rather than less. See In re Crowthers McCall Pattern, Inc., 120 B.R. 279, 300 (Bankr. S.D.N.Y. 1990). "[T]he 'adequate information' requirement merely establishes a floor, and not a ceiling for disclosure to voting creditors." Adelphia, 352 B.R. at 596 (citing Century Glove, Inc. v. First American Bank of New York, 860 F.2d 94, 100 (3d Cir. 1988)). "[O]nce the 'adequate disclosure' floor is satisfied, additional information can go into a disclosure statement too, at least so long as the additional information is accurate, and its inclusion is not misleading." Adelphia, 352 B.R. at 596.

19. As set forth below, the Disclosure Statement falls far short of its statutory purpose because it omits the most basic information on the impact of the PI TDP on the NAS Children, critical information to the thousands of claims filed on behalf of the NAS Children. While the Disclosure Statement states that "The Ad Hoc Group of Individual Victims has performed a

preliminary analysis that estimates that a qualified personal injury claimant will likely receive between $3,500 and $48,000 in distributions from such trust" (Disclosure Statement at §I.B), it does not state that, as applied to the NAS Children, the vast majority will not be entitled to **any** recovery, foreshadowing a trust distribution procedure which does not comport with traditional concepts of recovery under tort law and is so administratively complicated the trust corpus will primarily benefit the administrator as opposed to the victims.

20. All PI Claims will be dealt with only through the PI TDP, and the Debtors' vague description of the claims process is unacceptable. In other words, the PI TDP is binding on all creditors subject to the Plan. See Plan at 5.7(g) ("The Creditor Trustees shall determine the eligibility, amount and Allowance (if applicable) of the applicable Channeled Claims, in accordance with, and to the extent provided in, the applicable Creditor Trust Documents. In accordance with the trust distribution procedures and other provisions of the applicable Creditor Trust Documents, the Creditor Trustees shall also make all determinations with respect to Distributions to be made by the applicable Creditor Trust, which shall be funded in accordance with the Public Entity Settlements and the Private Entity Settlements, as applicable. The foregoing determinations by the applicable Creditor Trustee shall be final and binding and shall not be subject to any challenge or review of any kind, by any court or other Person, except as set forth in the Creditor Trust Documents"). While the Disclosure Statement contains a summary of the PI TDP, it either omits or fails to include the following critical information in a clear and concise matter:

- Detailed descriptions of eligibility criteria;
- That the List of "Qualifying Drugs" excludes many drugs;[14]

[14] See Bickford Declaration at ¶ 7-12.

- Basis of the "scoring grid" criteria for assigning "points" to different compensable injuries;[15]

- Description of required medical causation evidence and the standard of review applied;

- Scope of pharmaceuticals manufactured, licensed, rebranded or patented by a Purdue entity which will be considered and to what extent Purdue's joint and several liability, as it would be subject to under the normal scheme of tort law, is applicable to claims, either children or adults;

- An estimate of administrative costs that will be incurred to seek court approval of settlements with NAS Children, which costs may be significant; and

- An estimate of certain fees to be paid to counsel to the adult PI Claimants.[16]

Without this information, creditors lack the sufficient information to determine the nature of their recoveries or how their claims will be liquidated and paid.

II. The Solicitation Procedures Motion does not Provide a Mechanism to Vote the NAS Monitoring Claim

21. The Solicitation Procedures Motion does not contain any procedures whereby the holder of the Class 9 NAS Monitoring Claim may vote to accept or reject the Plan. Instead, the Debtors appear to believe individual claimants can vote in Class 9. The NAS Abatement Trust does not directly benefit any individual claimant. It is instead intended for the benefit of the NAS Children or their guardians. Thus, the NAS Monitoring Claim is more akin to a class claim, as set

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[15] The Disclosure Statement contains no disclosure on the statistical sample and modeling analysis. Instead, it merely states that "[t]he scoring grid, detailed in the TDP, was developed using statistical sampling and modeling performed by financial analysts and experts, based on scoring grids developed incomparable cases, and with unique customization based on the injuries suffered by victims of Purdue's opioid products and activities related thereto…" See Disclosure Statement at Article III.T.1 (emphasis added).

[16] See Disclosure Statement at Article III.T.1("The amount of the PI Trust Funds available to make settlement payments to holders of qualifying opioid-related personal injury claims from the PI Trust **will be subject to certain deductions, including for the fees and expenses of administering the TDP**…Those deductions include, but are not limited to, the amount of fees and expenses of…(vii) professionals representing the Ad Hoc Group of Individual Victims, and (viii) other employees of the PI Trust as well as outside legal, financial, accounting, investment, auditing, forecasting, and other consultants, advisors, and agents…") (emphasis added).

forth in the NAS Class Motion, than a claim for any individual claimants. As such, a proper representative should be designated, with the approval of the parties and the Court, solely for the purpose of voting the NAS Monitoring Claim.

22. Recognizing this issue, the Insys court entered a non-precedential stipulation (In re Insys Therapeutics, Inc., Case No. 19-11292 (KG) (Bankr. D. Del. Dec. 5, 2019) [Docket No. 962], a copy of which is attached to the Bickford Declaration as Exhibit A) that provided for an allowed NAS claim for all plan purposes. While non-precedential, because no party has proposed a viable alternative, the NAS Class Motion in this matter should be easily and readily resolved in similar fashion, and the designated class representative should be the only party permitted to vote the Class 9 NAS Monitoring Claim. Such a resolution will have the added benefits of eliminating: (i) the need to send multiple ballots to the caregivers for the NAS Children; and (ii) the potential for confusion amongst these caregivers, some, if not most, of whom are not as sophisticated as an ordinary creditor but who will nevertheless receive ballots for two different classes between which they must distinguish.

III. The Disclosure Statement Cannot be Approved because the Plan, as Currently Constituted, is Unconfirmable

23. The Disclosure Statement describes a plan that is unconfirmable on its face and therefore should not be approved. See, e.g., In re 266 Washington Assocs., 141 B.R. 275, 288 (Bankr. E.D.N.Y. 1992) ("A disclosure statement will not be approved where, as here, it describes a plan which is fatally flawed and thus incapable of confirmation."); In re Am. Capital Equip., LLC, 688 F.3d 145, 154 (3d Cir. 2012) ("Courts have recognized that if it appears there is a defect that makes a plan inherently or patently unconfirmable, the Court may consider and resolve that issue at the disclosure stage before requiring the parties to proceed with solicitation of acceptances and rejections and a contested confirmation hearing.") (internal quotations and citations omitted).

24. In fact, if the Plan on its face cannot be confirmed, approval of the Disclosure Statement must be denied in order to prevent the diminution of estate assets that would result from the expense of soliciting votes and seeking confirmation on a unconfirmable plan. See, e.g., In re Pecht, 57 B.R. 137, 139 (Bankr. E.D. Va. 1986) ("If, on the face of the plan, the plan could not be confirmed, then the court will not subject the estate to the expense of soliciting votes and seeking confirmation").

25. The Plan is patently unconfirmable on its face in that it improperly classifies NAS Children in the same category as holders of all other types of personal injury claims. In addition to such deficiency, the PI TDP is heavily and unfairly weighted in favor of adult personal injury claimants, to the detriment of the NAS Children.

A. The Plan Violates Section 1122 of the Bankruptcy Code Because the NAS Children's Claims are Wholly and Distinctly Separate from Adult Personal Injury Claims and Therefore Must be Separately Classified from Such Claimants

26. As detailed below, children who are born opiate dependent and are diagnosed with NAS go on to face life-long disabilities of delayed development and learning problems as a result of the fetal exposure to opioids they neither consumed nor consented to.[17] They may further present with teratogenic injuries to their vision and organs. In the tort system, most of these children are not constrained by statute of limitations until they reach majority. They are not faced with legal defenses of comparative fault or contributory negligence. They do not lose jobs or relationships, nor do they relapse into further opioid dependence or seek relief for their dependence through access to unprescribed drugs. In short, their injuries are completely distinct and their

[17] Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. BMC Psychiatry 2014;14:104.

situation within the legal system is not comparable to situational damages occasioned by adult victims.

27. Section 1122(a) of the Bankruptcy Code provides that "a plan may place a claim or an interest in a particular class only if such claim or interest is substantially similar to the other claims or interests of such class." 11 U.S.C. § 1122(a); see also In re Sabine Oil & Gas Corp., 555 B.R. 180, 310 (Bankr. S.D.N.Y. 2016); In re LightSquared Inc., 513 B.R. 56, 82 (Bankr. S.D.N.Y. 2014). Put another way, substantially different claims may not be placed in the same class. In this case, all claims of NAS Children are classified with all other personal injury claims in Class 10 of the Plan. However, the claims of the NAS Children are not substantially similar to all other personal injury claims.

28. There is precedent for classifying personal injury claimants in separate classes. For example, in In re Dow Corning Corp., 280 F.3d 648 (6th Cir. 2002), the Sixth Circuit held that classifying "foreign claims" differently from domestic claims was acceptable under section 1122 of the Bankruptcy Code. In that case, the Sixth Circuit affirmed the bankruptcy court's separate classifications because "without question, the evidence on the record shows that tort recoveries in the United States tend to be significantly higher than those in foreign jurisdictions." Id. at 662. Likewise, tort recoveries by permanently injured NAS Children who involuntarily ingested opioids will be higher than those of adults claiming the temporary condition of addiction due, in large point, to their voluntary ingestion of opioids.

29. The Debtors' failure to properly classify the NAS Children separately from general holders of personal injury claims is directly at odds with section 1129(a)(1) of the Bankruptcy Code's requirement that the Plan comply with the applicable provisions of the Bankruptcy Code, as well as section 1129(a)(2)'s requirement that the Debtors comply with all applicable provisions

of the Bankruptcy Code. 11 U.S.C. § 1129(a)(1). "The phrase 'applicable provisions' has been interpreted to include sections 1122 and 1123 of the Bankruptcy Code, which govern the classification of claims and interests and the contents of a chapter 11 plan." In re Aegerion Pharm., Inc., 605 B.R. 22, 30 (Bankr. S.D.N.Y. 2019). Here, the NAS Children's claims are fundamentally different than all other unsecured claims and may not be placed into the same class as the other personal injury claims.

1. Contributory Fault

30. The factual and legal merits of the claims of NAS Children are superior to those of the claims asserted by all other personal injury claimants. For example, unlike adult personal injury claimants, no NAS Child voluntarily used or ingested any opioid. This fact presents an inherent and irreconcilable difference between the claims of adults, whose damages are subject to comparative negligence reduction[18] or contributory negligence bar,[19] or wrongful conduct bar,[20]

[18] See, e.g., Tug Valley Pharmacy, LLC v. All Plaintiffs Below In Mingo Cty., 235 W. Va. 283, 291–93, 773 S.E.2d 627, 635–37 (2015) (finding addicts subject to comparative fault doctrine in their cases against pharmacies and healthcare providers for negligently dispensing controlled substances, including Lortab, Oxycontin and Xanax); Weaver v. Lentz, 348 S.C. 672, 683–85, 561 S.E.2d 360, 366-67 (Ct. App. 2002) (finding addict 50% at fault under comparative fault doctrine in wrongful death case against doctor for negligently prescribing controlled substances); Clair v. Paris Rd. Drugs, Inc., 573 So. 2d 1219, 1224-26 (La. Ct. App.) (finding addict 35% at fault under comparative fault doctrine in case against pharmacy and pharmacist for negligently dispensing controlled substances), writ denied, 577 So. 2d 31 (La. 1991).

[19] The doctrine of contributory negligence remains a complete bar to a plaintiff's claim in four States – Alabama, Maryland, North Carolina, and Virginia – and the District of Columbia. Contributory Negligence, 2 Jones on Evidence, §9.3 (7th ed. 2020). The remainder of the States have adopted the doctrine of comparative negligence, statutorily or by common law, which reduces the plaintiff's recovery proportionate to the degree of his or her fault. Id. However, as discussed infra, some of those states employ the wrongful conduct rule, which acts as a complete bar to recovery

[20] Some States recognize the wrongful conduct rule as a complete bar to a plaintiff's claims when those claims arise from the plaintiff's own illegal conduct, including in cases where the plaintiff illegally procured and used controlled substances. See, e.g. Price v. Purdue Pharma Co., 920 So. 2d 479, 484-86 (Miss. 2006) (wrongful conduct rule precluded plaintiff from pursuing tort claims against doctors, pharmacies and drug manufacturers for injuries sustained from ingesting OxyContin where he illegally procured the drug through fraud, deception and subterfuge); Foister v. Purdue Pharma, *L.P.*, 295 F. Supp. 2d 693, 704-05 (E.D. Ky. 2003) (same for plaintiffs who illegally procured and used OxyContin); Orzel by Orzel v. Scott Drug Co., 449 Mich. 550, 559-77, 537 N.W.2d 208, 212-21 (1995) (same for plaintiff's claim against pharmacy where he illegally procured and used controlled substance that caused him injury); Pappas v. Clark, 494 N.W.2d 245,247-248 (Iowa Ct. App. 1992) (same for wife's wrongful death

and the claims of NAS Children who, with no attendant fault, were born dependent upon opioids. In fact, jurisdictions across the country actually protect the interests of children by foreclosing the defense that a parent contributed to the child's injury through her tortious conduct.[21]

2. Unlike Adult Claims, the Claims of Most NAS Children are not Barred under Applicable Statutes of Limitations

31. Placing the NAS Children in the same class as other adult personal injury claimants is fundamentally unfair for many reasons. First, as a general matter, minority or infancy tolls a statute of limitations, such that the same does not run against a NAS Child during his or her minority.[22] *Infancy Suspending Limitations Period, Generally*, 54 C.J.S. Limitations of Actions § 161. In contrast to the claims of NAS Children, the limitations period applicable to an adult claimant in most states begins to accrue on the date of injury or, at the latest, on the date on which the claimant should have reasonably discovered the injury. Hence, the claims of most NAS Children are not burdened by limitations defenses the Debtors have prevailed on in all but one published case where the courts have considered their statute of limitations defense.[23]

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claim against pharmacy and other healthcare providers where husband illegally procured and used prescription drugs that led to his addiction and death).

[21] See, e.g. Ruffing ex rel. Calton v. Union Carbide Corp., 186 Misc. 2d 679, 682–90, 720 N.Y.S.2d 328, 330-36 (Sup. Ct. 2000) (per state statute, neither contributory nor comparative negligence of parents in exposing child to harmful chemicals *in utero* could be imputed to child for his personal injury claims against corporate defendants for the same exposure); Harrison v. United States, 233 F. Supp. 2d 128, 135 (D. Mass. 2002) (per state statute, mother's comparative negligence could not be imputed to child for assessment of damages in child's claim for personal injury); Byrne v. Schneider's Iron & Metal, Inc., 190 Mich. App. 176, 189, 475 N.W.2d 854, 860 (1991) (finding "comparative negligence of the parent may not be imputed to the recovery attributable to the child's damages"); Kochian v. Central Conn. Coast YMCA, No. CV075011527S, 45 Conn. L. Rptr. 351, 355–57, 2008 WL 1735587, *3-6 (Conn.Super. Mar. 31, 2008) (barring defendants from asserting parental comparative negligence in an effort to diminish minor plaintiff's recovery); Francis ex rel. Goodridge v. Dahl, 107 P.3d 1171, 1173 (Colo. App. 2005) ("Colorado has long refused to sustain the doctrine that the contributory or comparative negligence of the parents of a child of tender years shall be imputed to the child."); Shafer v. Spencer Hosp., 10 Pa. D. & C.4th 276, 280 (Com. Pl. 1991) ("The law is quite clear in Pennsylvania that an alleged negligent act or omission of a parent may not be imputed to his or her child to bar or reduce the minor's claims[,]" including the claims of a minor injured *in utero*).

[22] Only the following eight States do not recognize tolling of statutes of limitation during the period of minority or infancy: California, Connecticut, Delaware, Florida, Idaho, Illinois, Louisiana, and Virginia. https://www.statuteoflimitation.info/statute-of-limitations-minors.html#, last visited 3/19/2021, 4:34 p.m. EST.

[23] Yurcic v. Purdue Pharma, L.P., 343 F. Supp. 2d 386, 394 (M.D. Pa. 2004); Freund v. Purdue Pharma Co., No. 04-C-611, 2006 WL 482382, at *7 (E.D. Wis. Feb. 27, 2006); McKnight v. The Purdue Pharma Company, 2005

32. Although some states recognize a "discovery rule" exception to statutes of limitations or repose, this exception likely does not apply to the adult personal injury claims given that, in 2008, certain Debtors pled guilty to criminal charges involving the very acts and omissions that form the basis of the adult personal injury claims in this bankruptcy, and where Purdue's role in creating the opioid crisis has been well documented.[24] In fact, by 2010, there were well over 100 published lawsuits against the Debtors alleging the same theories and facts as the adult personal injury claimants in this bankruptcy.[25] This is in addition to over one thousand injury and death cases filed against the Debtors which were consolidated in New York state court in 2005 and which the Debtors settled in 2007.[26]

33. It is impossible to discern from the face of the proofs of claim how many of the adult personal injury claims are unenforceable as a matter of law because proofs of claim did not call for the identification of any dates of injury (or death) or ingestion of relevant drugs. However, on information and belief, that number reaches the tens of thousands (if not the majority) of adult personal injury claims, none of which appear to be excluded from payment under the proposed PI TDP.

WL 3115276, Civ. A. No. 9:04-CV-116 (E.D.Tex. Nov.21, 2005); Franz v. Purdue Pharma Co., No. 05-CV-201-PB, 2006 WL 455998, at *3 (D.N.H. Feb. 22, 2006); Foister v. Purdue Pharma, L.P., 295 F. Supp. 2d 693, 708 (E.D. Ky. 2003); Gallina v. Purdue Pharma Co., No. 05-2380, 2006 WL 8434665, at *4 (W.D. Tenn. Apr. 28, 2006); Boysaw v. Purdue Pharma, No. 1:07CV00079, 2008 WL 2076667, at *1 (W.D. Va. May 16, 2008).

[24] Meier, "U.S. Maker of OxyContin Pain Killer to Pay $600 Million in Guilty Plea," New York Times, May 11, 2007. https://www.nytimes.com/2007/05/11/business/worldbusiness/11iht-oxy.1.5665287.html?searchResultPosition=6 (last accessed April 1, 2021).

[25] See generally Richard C. Ausness, *The Role of Litigation in the Fight Against Prescription Drug Abuse*, 116 W. Va. L. Rev. 1117 (2014).

[26] In re OxyContin II, 23 Misc. 3d 974, 975, 881 N.Y.S.2d 812, 813 (Sup. Ct. 2009), rev'd sub nom. In re Oxycontin II, 76 A.D.3d 1019, 908 N.Y.S.2d 239 (2010). The TDP does not disqualify adult personal injury claimants who previously released their claims against Purdue in earlier settlements.

34. Thus, there is no justification for placing the NAS Children in the same class as thousands of adult personal injury claimants who could not recover outside the Plan. Moreover, unlike the NAS Children, adult personal injury claimants would be barred from filing claims under applicable non-bankruptcy law due to the expiration of the applicable statutes of limitation in their respective jurisdictions.

35. These same laws that toll the minors' statutes of limitation during their infancy also render the release and channeling provisions of the plan unenforceable with respect to all NAS Children under the age of 18 as of the Effective Date.

3. NAS Children Have Claims Based on Different Theories of Liability than All Other Personal Injury Claimants

36. Adult personal injury claims are based on the product liability theory the Debtors' marketing, lobbying, and sales efforts of Purdue branded prescriptions targeted vulnerable populations in such a manner as to spur a nationwide opioid crisis to profit the Debtors and the Sacklers. The effects of which the adult personal injury claimants are complaining of are clearly listed in the labels triggering the learned intermediary defense.

37. However, the NAS Children's claims are based on civil conspiracy. Specifically, the NAS Children's claims arise from the allegation that Purdue initiated, led, and financed a civil conspiracy that deceived regulators, expectant mothers, women of child-bearing age, and their physicians by hiding and failing to report its scientific knowledge regarding the dangers which opioid use presented to developing fetuses.[27] That is, Purdue hid or ignored evidence of studies,

[27] Scott Bickford, Esq., *Purdue Bankruptcy Joint NAS Proof of Claim, Question 10- Basis of Claim,* PrimeClerk Electronic Filings 7/15/2020, 7/22/2020, 7/28/2020 & 7/29/2020.

some by its own scientists, that causally linked fetal opioid exposure to birth defects and other congenital malformations.[28]

38. Because the Debtors cannot meet the requirements of section 1129(a)(1) and (a)(2) of the Bankruptcy Code, the Plan is patently unconfirmable.

B. Because the TDP Treats NAS Children Differently than Other Personal Injury Claimants, the PI TDP Violates Section 1123(a)(4) of the Bankruptcy Code.

39. While the NAS Ad Hoc was involved in certain discussions and negotiations (primarily with respect to the negotiation of the NAS Monitoring Trust Documents), the PI TDP was negotiated by counsel for the adult personal injury claimants and the public entities without the participation of the NAS Ad Hoc.[29] Based on a cursory review of the PI TDP,[30] it clearly treats the NAS Children dramatically different than other similarly situated personal injury Claimants in contravention of section 1123(a)(4) of the Bankruptcy Code, which provides that "(a) [n]otwithstanding any otherwise applicable nonbankruptcy law, a plan shall—(4) provide the same treatment for each claim or interest of a particular class, unless the holder of a particular claim or interest agrees to a less favorable treatment of such particular claim or interest." 11 U.S.C. § 1123(a)(4).

40. Neither the Code nor its legislative history precisely defines the standards for "equal treatment." In re Adelphia Commc'ns Corp., 368 B.R. 140, 249 (Bankr. S.D.N.Y. 2007).

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[28] Supra, Broussard; Purdue OxyContin New Drug Application Reproductive Toxicology Studies: DSE-058, DSE-059, DSE-060, DSE-061.

[29] The claims administrator under the PI TDP will be Ed Gentle. See Disclosure Statement at Article III.T.1. The NAS Ad Hoc reserves its right to object to Mr. Gentle as the claims administrator on the grounds, among others, that he may not be an impartial adjudicator of the PI Claims. The NAS Ad Hoc reserves its right to object to Mr. Gentle as claims administrator to the extent of any conflicts of interest.

[30] As stated previously, the NAS Ad Hoc had an opportunity to review prior versions of the PI TDP but only a few days to review the filed PI TDP. The NAS Ad Hoc therefore reserves its right to supplement this Objection after it completes its review of the PI TDP.

"Even though neither the Code nor the legislative history precisely defines the standards of equal treatment, the most conspicuous inequality that § 1123(a)(4) prohibits is payment of different percentage settlements to co-class members." In re AOV Indus., Inc., 792 F.2d 1140, 1152 (D.C. Cir. 1986).

41. In this case, the NAS Children are classified with all other personal injury claimants in Class 10, and all are being channeled to the PI Trust. Plan at §4.10. Despite inclusion of NAS Children in the larger personal injury claimant group, the NAS Children are being treated dissimilarly, and as a direct result, a NAS Children will receive substantially less than a similarly situated, adult personal injury claimant. The PI TDP is unfairly prejudicial to NAS Children because: (a) the administrative burden on NAS Children is far higher than on other PI Claimants; (b) the PI Trustee's discretion is overly broad and excessive; and (c) the gating requirements are artificial and unfair to NAS Children.

42. In the event of approval of the PI TDP, these unreasonable impediments will result in the vast majority of NAS Children not receiving any distribution and the lowest possible distribution for those NAS Children that do receive a distribution, despite the serious nature of the permanent injuries that have been sustained by the NAS Children. In fact, the PI TDP is designed to not only favor all adult victims over NAS Children but likely favors one group of victims over all other victims, be they adult or children.

1. The PI TDP Imposes a Greater Administrative Burden on the NAS Children

43. Without a sound basis in tort law the PI TDP purports to arbitrarily and artificially require proof of a temporal relationship between the prescription of certain NDC-labeled Purdue opioids and the victim's first documented instance of addiction or substance abuse, that one of these drugs was used during the pregnancy or used for six months. See PI TDP at § 7(a)(i)(A)(2).

Simply put, in order to qualify under the PI TDP for any more than a minimum payment, a claimant must prove that a Purdue drug, as designated in the incomplete list of drugs, was the one drug which caused their very first addiction. Setting aside whether the distinction between a first addiction or subsequent exposures is meaningful, if first addiction can possibly be discerned with a reasonable degree of medical certainty, the subjective nature of the diagnosis of "first addiction" (dependency or substance abuse) will require extensive medical records or expert reports. Further, with respect to adult personal injury claimants, the occurrence of an assortment of subjective conditions or events in the claimant's life, to which conditions or events the PI TDP enhances the value of adult claims. This analysis applied to some purported 135,000 claims is as byzantine as it sounds and will lead to the sorting and dating of prescriptions by the PI Trustee, or more likely, to eschewment of such work by the PI Trustee in favor of the acceptance of the bald allegations in affidavits submitted by adults claiming addiction, which the PI TDP authorizes the PI Trustee to accept in lieu of objective documentary evidence. See PI TDP at § 5(g). Further, the drafters of the PI TDP have nimbly set up a temporality requirement which is illusory as to adult personal injury claimants who are authorized to offer factually uncorroborated affidavits to meet the temporality requirement.

44. The temporality burden is especially onerous, if not exclusionary, as applied to NAS Children. It has no relationship to the proof required under traditional applications of tort law. Unless the guardian is the birth mother of a NAS Child, the guardian has no legal right to acquire the birth mother's medical, pharmacy, or other records, but must nevertheless prove under the PI TDP that a prescribed Purdue opioid was **the** precipitating cause of the birth mother's addiction, that the birth mother used a Purdue-branded product during pregnancy or for more than six months. See PI TDP at §§ 7(a)(i)(A)(2)(bb); 7(a)(iii). Therefore, the PI TDP presents an

insurmountable and artificial burden of proof that cannot be met by guardians who have no legal right to the birth mother's records or who lack the birth mother's personal knowledge necessary to make out the affidavits required by the PI TDP in lieu of records. For this reason, and unless the PI TDP is fairly written, it is likely that most NAS Children, whose interests are represented by guardians that are not their birth mothers, will be relegated to "Easy Pay" or equally valued Tier 3, the lowest compensation payable under the PI TDP, if they manage to qualify for payment at all. See PI TDP at § 6. Thus, a "one-size fits all" approach to all personal injury claims under the PI TDP is neither appropriate nor fair as applied to NAS Children.

45. Further, even if the guardian of a NAS Child could produce the requisite affidavit(s), the drafters of the PI TDP demonstrate their prejudice against NAS Children by prohibiting the submission of an affidavit to establish a claim under Tiers 1 and 2, *i.e.,* those levels at which NAS Children with the most serious injuries would receive higher compensation. See PI TDP at § 7(a)(i)(C) and 7(a)(iii)(C). It is obvious that the PI TDP is designed to drive any surviving claims by NAS Children toward no reasonable distribution at all and to force them to accept "Easy Pay," despite the permanency and degree of the injuries NAS Children have sustained.

46. The NAS Ad Hoc analyzed comprehensive data from a leading health insurer as a means of projecting the impact of the PI TDP on NAS Children. See Bickford Declaration at ¶ 13. Based on such analysis, sixty-five (65) out of every eighty-two (82) NAS Children, approximately eighty percent (80%) of all NAS Children, will be ineligible for any payment under the PI TDP – this extrapolates to 5,211 NAS Children of the 6,514 that filed proofs of claim. Id. at ¶ 14. Only twenty percent (20%) of NAS Children might be able to receive an award, and only 7% may be eligible to receive anything higher than the $3,500.00 of easy pay that the PI TDP affords. Id. at ¶ 14-15. Within the ninety-three percent (93%) of NAS Children who will receive nothing or be

forced to accept easy pay are children who were born with birth defects and/or have permanent brain damage or developmental impairments. Id. at ¶ 15.

47. This is in part because the PI TDP ties an individual's right to compensation to exposure to a Purdue product, as if Purdue's only source of liability to individuals whose lives were destroyed by Purdue's role in the opioid crisis is products liability. This artificial bar to recovery is unique to individuals in that no other class of creditor, public or private, is compelled to prove that its harm resulted from a Purdue product. For instance, the hospitals and third-party payors are recovering hundreds of millions of dollars under the Plan for the same causes of action (*e.g.*, conspiracy, nuisance) held by thousands of NAS Children who will receive little or no compensation under the Plan. Moreover, no public entity (state or municipality) is required to demonstrate causation directly related to a Purdue product in order to recover under the Plan. As applied to individuals but no other creditor, the PI TDP completely ignores Purdue's outsized role in creating the opioid crisis relative to its market share.

48. Further, in the event that state-court approval is required for the approval of claims given to minors, collection of amounts received by NAS Children under the PI TDP, no NAS Child receiving the meager "easy pay" could economically justify the cost of such state court approval. In sum, based on the NAS Ad Hoc's analysis of the PI TDP, the NAS Children would receive no more in the aggregate than approximately $5,676,000 [$1/point, See PI TDP §8(b)] in the aggregate, which is a mere fraction (0.7%) of the $750 million fund the Debtors and public creditors have promised to representatives of the adult personal injury claimants. This comes nowhere close to equity with respect to NAS Children.

2. Gating Requirements Unfairly Disadvantage NAS Children

49. The PI TDP unfairly requires information not sought on the Proof of Claim form, which works to the disadvantage of NAS Children who either filed *pro se* or who lack, in many instances, the ability to acquire documentary evidence to establish temporality.

50. The prejudicial treatment of NAS Children extends to the tiering structure of the PI TDP Tiers 1 and 2 impose on NAS Children medical and causation requirements which exceed those placed on adult personal injury claimants alleging addiction to opioids. For instance, if a NAS Child makes a claim under Tier 1, the PI TDP requires the child's guardian provide, to the satisfaction of the PI Trustee, medical documentation and scientific literature to establish a causal link between opioids and the injury alleged. See PI TDP at § 7(a)(i)(C)(4).

51. Additionally, in order to qualify for a Tier 2 award, the PI TDP requires six or more months of opioid usage by the birth mother of a NAS Child. See PI TDP at § 7(a)(iii). This is an artificial restriction which has no basis in tort law nor is there a medical or scientific basis for such requirement, given that NAS and injuries related thereto are caused by less than six months of fetal opioid exposure. Presumably the Debtors propound the six-month period of Purdue opioid usage in an effort to establish a dose-response relationship. Given that all NAS Children must put forward evidence of opioid withdrawal symptoms at birth this arbitrary six-month exposure approach fails because "there are no questions of [fetal] opioid dose to address… all had significant exposure to pre-natal opioid pharmaceuticals via their mother. This was at a level which subsequently led to the postpartum diagnosis of NAS."[31]

[31] *Dr. C.V. Howard's Declaration in Support of Class Certification* (attached to the Bickford Declaration as Exhibit C) at 18.

52. "The six month temporal relationship requirement between use of a qualifying product and the onset of addiction, dependence or substance abuse" is arbitrary, bears no relation to the science of addiction and is contrary to the state of the art medical practice for the diagnosis of OUD set forth in the DSM-V.[32] Moreover, the PI TDP overreaches, to the prejudice of NAS Children, in favor of adult personal injury claimants by allowing them to potentially double recover, an option which is unavailable to NAS Children. Under the PI TDP, an adult alleging addiction may "double dip" by recovering a base payment for "addiction, dependence, or substance abuse" and also an enhanced monetary award for "opioid use disorder" under Tier 1. See PI TDP at § 7(a)(i)(B)(1)(aa). This provision is nonsensical because the foregoing conditions are one and the same. In addition, the Tier 1 level award based on "OUD diagnosis" and "Death" do "not have to coincide in time to the provided qualifying product use," an exception so inconsistent that, with respect to adult personal injury claimants, it completely writes the temporality requirement out of the PI TDP.[33] The PI TDP affords no such exception to NAS Children, all of whom are required to prove temporality, *i.e.*, exposure to a qualifying opioid during the period of gestation to qualify for Tier 1.

53. In a final affront to NAS Children, the PI TDP affords significant rights of recovery to opioid addicted minors who voluntarily ingested "non-prescribed versions of a qualifying opioid," (presumably diversionary market drugs) whereas NAS Children, who did not voluntarily ingest anything, have no such recourse and are instead required to prove ingestion by the birth mother of a prescribed qualifying opioid within a tight temporal window to qualify for Tier 1. Compare PI TDP at § 3(a)(i) with PI TDP at § 7(a)(i)(A)(2).

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[32] *Expert Report of Dr. Gregory Skipper, MD* (attached to the Bickford Declaration as Exhibit D) at ¶ 22-27.

[33] Id.

3. The PI TDP Grants Overly Broad and Excessive Discretion to the PI Trustee

54. With respect to NAS Children, the PI TDP vests the PI Trustee with overly broad and excessive discretion. The PI TDP requires that each NAS Child asserting "serious" injury submit data establishing scientific causation to the PI Trustee. See PI TDP at § 7(a)(i)(B)(2)(bb). In such regard, the PI TDP grants sole discretion to the PI Trustee to determine whether sufficient scientific evidence has been presented and whether there is a reasonable scientific basis for making an award. The drafters of the PI TDP do not, of course, impose this burden of proof on adult personal injury claimants or grant the PI Trustee similar discretion with regard to causation analysis of adult personal injury claims.

C. The Plan Violates Section 1129(a)(3) because it was not Proposed in Good Faith

55. Section 1129(a)(3) of the Bankruptcy Code requires a bankruptcy court to deny confirmation of a plan if it is not proposed in "good faith" or contains provisions "forbidden by law." 11 U.S.C. § 1129(a)(3). The Second Circuit has construed the good faith standard as requiring a showing that "the plan was proposed with honesty and good intentions and with a basis for expecting that a reorganization can be effected." Kane v. Johns-Manville Corp. (In re Johns-Manville Corp.), 843 F.2d 636, 649 (2d Cir. 1988) (internal quotations omitted); see also In re Texaco, Inc., 84 B.R. 893, 907 (Bankr. S.D.N.Y. 1988) ("[I]n the context of a [Chapter 11] reorganization . . . a plan is considered proposed in good faith if there is a likelihood that the plan will achieve a result consistent with the standards prescribed under the [Bankruptcy] Code.") (internal quotations omitted). Additionally, courts generally hold that "good faith" should be evaluated in light of the totality of the circumstances surrounding confirmation. In re Cellular Info. Sys., Inc., 171 B.R. 926, 945 (Bankr. S.D.N.Y. 1994).

56. Here, as set forth above, the Plan violates section 1122 of the Bankruptcy Code by not separately classifying the NAS Children, and despite placing NAS Children and all other personal injury claimants in the same class, the Plan violates section 1123 of the Bankruptcy Code by failing to treat NAS Children the same as all other personal injury claimants. Therefore, the Plan cannot "achieve a result consistent with the standards prescribed under the [Bankruptcy] Code." Texaco, 84 B.R. at 907.

D. The Plan Releases are Inappropriate Under the Circumstances

57. While the NAS Ad Hoc concedes that objections to the Plan's release provisions are appropriately asserted in connection with confirmation of the Plan, it is necessary to draw the Court's attention to an issue which is of constitutional magnitude. The term "Causes of Action" in the Plan "expressly includes (i) any Cause of Action held by a natural person who is not yet born or who has not yet attained majority as of the Petition Date or as of the Effective Date." Plan at § 1.1. Section 10.6 of the Plan further provides that all Releasing Parties (which includes all Holders of Claims and Interests), shall release the Released Parties from any and all "Causes of Action." Plan at § 10.6(b). With respect to the unborn, such release provisions are patently unconstitutional because, by definition, an unborn NAS Children has yet to sustain any opioid-related injury.

58. Notice and an opportunity to be heard are fundamental requisites of the constitutional guarantee of procedural due process, Eisen v. Carlisle & Jacquelin, 417 U.S. 156, 174 (1974), a guarantee which applies to the discharge of claims in bankruptcy court. City of New York v. New York, New Haven & Hartford R.R. Co., 344 U.S. 293, 296-97 (1953). To satisfy due process, "notice must be reasonably calculated, under all circumstances, to apprise interested

parties of the pendency of the action and afford them an opportunity to present their objections." Mullane v. Cent. Hanover Bank & Tr. Co., 339 U.S. 306, 314 (1950).

59. Over two decades ago, the Supreme Court cautioned against what this Plan proposes – an order that binds those "with no perceptible … disease," including those who "may not even know of their exposure, or realize the extent of the harm they may incur." Amchem Prods., Inc. v. Windsor, 521 U.S. 591, 628 (1997) (involving a global settlement seeking to resolve both current and future asbestos-related claims). Under principles of due process, one who does not receive adequate notice of bankruptcy proceedings, and whose claims are "abstract, unimaginable, and inchoate at the time," is not enjoined by an order of the bankruptcy court. In re Johns-Manville Corp., 600 F.3d 135, 158 (2d Cir. 2010). The NAS Ad Hoc respectfully submits that, as to unborn future NAS Children who can sustain no injury until birth, there is no notice pertinent to the Plan, or the right to object thereto, which could comport with due process and be deemed constitutionally sufficient.

60. The Plan definitions also offend Article III of the United States Constitution, in that future NAS Children who have not been born or sustained injury lack any justiciable "claim or controversy" as required by Article III. Article III preserves the separation of powers by confining federal courts to their proper adjudicative function and preventing advisory opinions that would intrude on the legislative and policy-making functions that the Constitution assigns to Congress and the President. Lujan v. Defenders of Wildlife, 504 U.S. 555, 559-60 (1992). Unaccrued, contingent tort claims of yet-to-be-born NAS Children do not meet the requirements of Article III, and the Plan's request that the Bankruptcy Court adjudicate the rights of such claimants undermines the adversarial system that Article III preserves.

61. Moreover, the Plan contains broad third-party, non-debtor releases (including with respect to the Sackler Family) that may be inappropriate under the circumstances of these chapter 11 cases. The NAS Ad Hoc joins and incorporates the *Objection of United States Trustee to Disclosure Statement for Chapter 11 Plan of Purdue Pharma, L.P. and its Affiliated Debtors* [Docket No. 2686], with respect to the Sackler family releases, proposed third-party releases and injunction, and the proposed discharge of the Debtors.

RESERVATION OF RIGHTS

62. Nothing contained herein shall constitute a waiver of any rights or remedies of the NAS Ad Hoc under title 11 of the United States Code or applicable law, including, without limitation, the right to: (i) amend, modify, or supplement this Objection, or (ii) raise any other additional arguments at a later date, including, but not limited to, in an objection to the Plan,

CONCLUSION

63. The NAS Ad Hoc respectfully requests that the Court not approve the Disclosure Statement and deny the Solicitation Procedures Motion.

Dated: New York, New York
April 26, 2021

TARTER KRINSKY & DROGIN LLP
Counsel for NAS Ad Hoc Committee

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EXHIBIT 1

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UNITED STATES BANKRUPTCY COURT
SOUTHERN DISTRICT OF NEW YORK

In re:	:	Chapter 11
PURDUE PHARMA L.P., *et al*.,	:	Case No. 19-23649 (RDD)
Debtors.[1]	:	(Jointly Administered)

DECLARATION OF SCOTT R. BICKFORD, ESQ. IN SUPPORT OF THE NAS CHILDREN AD HOC COMMITTEE'S *LIMITED OBJECTION TO DISCLOSURE STATEMENT AND SOLICITATION PROCEDURES* MOTION

Under 28 U.S.C. § 1746, I, Scott R. Bickford, declare under the penalty of perjury that the following is true and correct to the best of my knowledge, information, and belief:

1. This declaration ("Declaration") is submitted in support of *The NAS Children Ad Hoc Committee's Limited Objection to Disclosure Statement and Solicitation Procedures Motion*.

[1] The Debtors in these cases, along with the last four digits of each Debtor's registration number in the applicable jurisdiction, are as follows: Purdue Pharma L.P. (7484), Purdue Pharma Inc. (7486), Purdue Transdermal Technologies L.P. (1868), Purdue Pharma Manufacturing L.P. (3821), Purdue Pharmaceuticals L.P. (0034), Imbrium Therapeutics L.P. (8810), Adlon Therapeutics L.P. (6745), Greenfield BioVentures L.P. (6150), Seven Seas Hill Corp. (4591), Ophir Green Corp. (4594), Purdue Pharma of Puerto Rico (3925), Avrio Health L.P. (4140), Purdue Pharmaceutical Products L.P. (3902), Purdue Neuroscience Company (4712), Nayatt Cove Lifescience Inc. (7805), Button Land L.P. (7502), Rhodes Associates L.P. (N/A), Paul Land Inc. (7425), Quidnick Land L.P. (7584), Rhodes Pharmaceuticals L.P. (6166), Rhodes Technologies (7143), UDF L.P. (0495), SVC Pharma L.P. (5717) and SVC Pharma Inc. (4014).

2. I am an attorney in good standing admitted to practice in the State of Louisiana. I make this Declaration based on my own personal knowledge and belief, and upon documents and information available to me as counsel to the NAS Children Ad Hoc Committee. Capitalized terms used but not defined herein shall have the meaning given to such term in the Objection or the PI Trust Distribution Procedures [Docket No. 2732, Ex. C], as the case may be.

3. Attached hereto as **Exhibit A**, filed together with this Declaration, is a true and accurate copy of a court ordered non-precedential stipulation from In re Insys Therapeutics, Inc., Case No. 19-11292 (KG) (Bankr. D. Del. Dec. 5, 2019) [Docket No. 962].

4. Attached hereto as **Exhibit B** filed together with this Declaration, is a true and accurate copy of the *Declaration of Dr. Kanwaljeet S. Anand*.

5. Attached as **Exhibit C**, filed together with this Declaration, is a true and accurate copy of *Dr. C.V. Howard's Declaration in Support of Class Certification.*

6. Attached as **Exhibit D**, filed together with this Declaration, is a true and accurate copy of the *Expert Report of Dr. Gregory Skipper, MD*.

A. Analysis of PI TDP Exhibit A's list of qualifying opioids

7. For a PI Claimant to qualify for any payment, they must provide approved documentation of a prescription opioid included on Exhibit A to the PI TDP, which consists of a list of NDC (National Drug Code) numbers:[2]

> § 3. INITIAL PI CLAIM ALLOWANCE.
>
> For a given PI Claim to qualify as an Allowed PI Claim, the applicable PI Claimant must, with respect to that PI Claim:

[2] A NDC number is a unique 3-segment number that is the universal product identifier for drugs in the US. The first segment of each NDC number identifies the labeler (such as the manufacturer, repackager or distributer). The second segment identifies the product (the strength, dosage form and formulation of a drug for a specific labeler). The third segment is the package code, identifying package sizes and types). Only the first two segments are included in the Exhibit A list, thus appearing as XXXXX-YYY-, as opposed to XXXXX-YYY-ZZ.

> (a) Demonstrate usage of a qualifying prescribed opioid[3] listed on Exhibit A hereto…

8. Many claims, including those of many NAS Claimants, are based upon prescribed generic and rebranded opioids linked to Purdue. For a Purdue linked generic opioid to qualify, the Claimant must provide documentation of a valid opioid prescription showing a corresponding NDC number in Exhibit A. PI TDP at § 4(b)(i) and § 5(a) – (e). The completeness of the list of NDC numbers is therefore paramount, as the PI TDP bars claims based upon generic opioids not on the list.[4]

9. A footnote to § 4(b)(i) acknowledges the importance of Exhibit A's completeness, stating that the Exhibit A list is "subject to additional NDC numbers after discovery from Debtors." Counsel is unaware of any such discovery being undertaken.

10. Counsel's preliminary comparison of the Schedule A list to other known NDC numbers for Purdue (labeler code 59011) and Rhodes (labeler code 42858) linked opioids reveals that the list is incomplete. For instance, at least two NDC numbers for Rhodes labeled generic opioid morphine sulphate, 42858-804- and 42858-805-, are inexplicably missing from Exhibit A.

11. Further, Exhibit A sporadically includes opioids for labelers beyond Purdue and Rhodes but omits other generic and rebranded opioids of the same type from those same labelers. Two NDC numbers for morphine sulphate labeled by Ranbaxy, for example, are included on Exhibit A, while seven are excluded.

---

[3] A lawful prescription is required for all but Claimants or birth mothers who were minors when they initiated usage of a non-prescribed version of a qualifying opioid in Exhibit A. § 3(a)(i).

[4] There are two exceptions to the bar on generic opioids not included in Exhibit A:

> (1) "A notation in the record that the product is labeled by Rhodes or [Purdue]" (PI TDP at § 4(b)(ii)); or
>
> (2) the generic opioids are Oxycodone CR or Oxycodone ER. PI TDP at § 4(c).

12. Exhibit A's list of qualifying opioids is clearly incomplete and will result in exclusion of otherwise valid claims as proposed.

B. Modeling of NAS Claim Eligibility and Awards under PI TDP

13. The NAS Ad Hoc Committee undertook an objective analysis of comprehensive data from a leading health insurer on the prescription histories of eighty-two (82) birth mothers. This sample of birth mother prescription data was objectively selected, as it includes all such data produced by the health insurer to counsel to date—no produced birth mother prescription data was omitted. The analysis involved comparing the TDP's requirements and list of qualifying opioids in Exhibit A to the PI TDP against the birth mothers' prescription histories and their children's medical histories in order to model the award outcomes for the NAS Children of these birth mothers under the proposed PI TDP.

14. The modeling revealed that only 17 of the 82 (20.7%) NAS Claimant Children would stand to receive any award under the PI TDP as proposed, meaning 65 of the children (79.3%) would be completely ineligible for any payment under the PI TDP. This ineligibility is the result of the exclusion of their birth mothers' prescriptions from the list of qualifying opioids under the PI TDP's Exhibit A despite the fact that the birth mother's prescriptions would meet the broader prescription list found on the Proof of Claim Form at question 14.

15. Of the 17 that qualified at all, only 6 (7.3%) qualified for anything above the minimum payment of $3,500. Only 2 (2.5%) qualified for Tier 1: 1 child qualified for Tier 1 Base, the other for Tier 1A. Only 4 qualified for Tier 2 (4.8%): 3 qualified for Tier 2A, the other for Tier 2B.

16. The NAS Ad Hoc Committee then modeled the value of these claims under the proposed PI TDP. The TDP assigns a set number of points to each claim based upon award tier,

and estimates a dollar award amount per point of between $0.80 and $1.20. Assuming the mid-point of these estimates, $1 per point, all NAS Children would receive no more in the aggregate than approximately $5,676,000—0.7% of the $750 million fund under the proposed PI TDP.

NEW ORLEANS, LA.

Respectfully submitted this 26th day of April, 2021:

/s/ Scott R. Bickford

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EXHIBIT A

IN THE UNITED STATES BANKRUPTCY COURT
FOR THE DISTRICT OF DELAWARE

In re	:	**Chapter 11**
INSYS THERAPEUTICS, INC., *et al.*,	:	**Case No. 19-11292 (KG)**
Debtors.[1]	:	**Jointly Administered**
	:	**Re: Docket No.** 628

ORDER APPROVING STIPULATION BY AND BETWEEN THE DEBTORS, THE OFFICIAL COMMITTEE OF UNSECURED CREDITORS, AND THE NAS BABY CLAIMANTS ESTABLISHING CLASS CLAIMS PROCEDURES

Upon consideration of the *Stipulation By and Between the Debtors, the Official Committee of Unsecured Creditors, and the NAS Baby Claimants Establishing Class Claims Procedures* (the "**Stipulation**"),[2] a copy of which is attached hereto as **Exhibit 1**; and the Court having jurisdiction to consider the Stipulation pursuant to 28 U.S.C. § 1334; and approval of the Stipulation being a core matter pursuant to 28 U.S.C. § 157(b)(2); and sufficient notice of the NAS Baby Class Claimants' Motions having been provided; and it appearing that no other notice of the same is required under the circumstances; and good and sufficient cause appearing therefor,

IT IS HEREBY ORDERED THAT:

1. The Stipulation is hereby approved.

2. Immediately upon the entry of this Order, the Stipulation shall become effective and the NAS Baby Class Claimants' Motions shall be deemed withdrawn without prejudice.

[1] The Debtors in these chapter 11 cases, along with the last four digits of each Debtor's federal tax identification number, as applicable, are: Insys Therapeutics, Inc. (7886); IC Operations, LLC (9659); Insys Development Company, Inc. (3020); Insys Manufacturing, LLC (0789); Insys Pharma, Inc. (9410); IPSC, LLC (6577); and IPT 355, LLC (0155). The Debtors' mailing address is 410 S. Benson Lane, Chandler, Arizona 85224.

[2] Capitalized terms used but not defined in this Order have the meanings used in the Stipulation.

3. The Parties are authorized to take any and all actions reasonably necessary to implement and effectuate the terms of the Stipulation.

4. This Court retains jurisdiction over all matters arising from or related to the implementation or interpretation of this Order.

Dated: December 5, 2019
Wilmington, Delaware

THE HONORABLE KEVIN GROSS
UNITED STATES BANKRUPTCY JUDGE

EXHIBIT 1

Stipulation

IN THE UNITED STATES BANKRUPTCY COURT
FOR THE DISTRICT OF DELAWARE

In re	:	**Chapter 11**
INSYS THERAPEUTICS, INC., *et al.*,	:	**Case No. 19-11292 (KG)**
Debtors.[1]	:	**Jointly Administered**
	:	**Re: Docket No. _____**

STIPULATION BY AND BETWEEN THE DEBTORS, THE OFFICIAL COMMITTEE OF UNSECURED CREDITORS, AND THE NAS BABY CLAIMANTS ESTABLISHING CLASS CLAIMS PROCEDURES

This stipulation (the "**Stipulation**") is made and entered into by and between Insys Therapeutics, Inc. and its affiliated debtors, as debtors and debtors in possession (collectively, the "**Debtors**"), the official committee of unsecured creditors (the "**Committee**"), and the NAS Baby Claimants[2] (collectively, the "**Parties**"), by and through their respective undersigned counsel.

RECITALS

WHEREAS, on June 10, 2019 (the "**Petition Date**"), each of the Debtors commenced with the United States Bankruptcy Court for the District of Delaware (the "**Court**") a voluntary case under chapter 11 of title 11 of the United States Code, 11 U.S.C. §§ 101-1532 (the "**Bankruptcy Code**");

WHEREAS, on August 22, 2019, the NAS Baby Claimants filed the *Amended Motion by NAS Baby Class Action Claimants Pursuant to Fed. R. Bankr. P. 9014 and 7023 to Make Federal*

[1] The Debtors in these chapter 11 cases, along with the last four digits of each Debtor's federal tax identification number, as applicable, are: Insys Therapeutics, Inc. (7886); IC Operations, LLC (9659); Insys Development Company, Inc. (3020); Insys Manufacturing, LLC (0789); Insys Pharma, Inc. (9410); IPSC, LLC (6577); and IPT 355, LLC (0155). The Debtors' mailing address is 410 S. Benson Lane, Chandler, Arizona 85224.

[2] The "**NAS Baby Claimants**" are represented by Amanda Hanlon, Walter and Virginia Salmons, and Christopher Bardsley.

Rule of Civil Procedure 23 Applicable to These Proceedings and to Permit the Filing of a Class Proof of Claim [Docket No. 513] (the "**First NAS Baby Class Claimants' Motion**") and on September 18, 2019, the NAS Baby Claimants filed the *Motion by NAS Baby Claimants That Have Duly Received a Notice to File Proof of Claim in This Matter Pursuant to Fed. R. Bankr. P. 9014 and 7023 to Make Federal Rule of Civil Procedure 23 Applicable to These Proceedings and to Permit the Filing of a Class Proof of Claim on Their Behalf* [Docket No. 628] (together with the First NAS Baby Class Claimants' Motion, the "**NAS Baby Class Claimants' Motions**").

NOW THEREFORE, THE PARTIES, BY AND THROUGH THEIR RESPECTIVE UNDERSIGNED COUNSEL, HEREBY STIPULATE AND AGREE AS FOLLOWS:

1. The above recitals are fully incorporated herein and made an express part of this Stipulation.

2. Upon approval of this Stipulation by the Court, (a) the NAS Baby Class Claimants' Motions shall be deemed withdrawn without prejudice, (b) the procedures attached hereto as **Exhibit 1-A** (as may be amended or supplemented by agreement of the Parties in connection with confirmation of the Proposed Plan (as defined below), the "**NAS Baby Class Claims Procedures**") with respect to holders of claims represented by the NAS Baby Claimants under the terms of the NAS Baby Class Claims Procedures and the Proposed Plan (the "**NAS Baby Class**") shall become binding upon the Parties hereto in these chapter 11 cases, and (c) NAS Baby Claimants in the NAS Baby Class shall file, within ten (10) business days of the approval of this Stipulation, a Proof of Claim on behalf of the NAS Baby Class (the "**NAS Baby Class Claim**"), which shall be the NAS Baby Class Claim with respect to which the Debtors, or any successor thereto, will make distributions under the Proposed Plan, if confirmed.

3. Subject to approval by the Court, the Parties consent, and waive any right to object, to incorporation of the terms of the NAS Baby Class Claims Procedures into the *Second Amended Joint Chapter 11 Plan of Liquidation of Insys Therapeutics, Inc. and Its Affiliated Debtors* [Docket No. 928] (as may be amended or modified from time to time, the "**Proposed Plan**") and the disclosure statement related thereto [Docket No. 929] (as may be amended or modified from time to time, the "**Proposed Disclosure Statement**"), and the Parties agree to be bound by such terms.

4. The NAS Baby Claimants may, upon written notice to the counsel for the Debtors and the Committee, terminate this Stipulation if any of the following shall occur: (i) the Proposed Plan (subject to non-material modifications) is not confirmed by the Court through and including the date of the expiration of the period during which the Debtors exclusively may file a plan (as the same may be extended from time to time); (ii) these chapter 11 cases shall be converted to cases under another chapter of the Bankruptcy Code; (iii) a trustee shall be appointed in these cases; or (iv) these cases shall be dismissed.

5. The Debtors, or any successor to the Debtors, may terminate this Stipulation on written notice to the NAS Baby Claimants if any of the following shall occur: (i) the Proposed Plan (subject to non-material modifications) is not confirmed by the Court through and including the date of the expiration of the period during which the Debtors exclusively may file a plan (as the same may be extended from time to time); (ii) these chapter 11 cases shall be converted to cases under another chapter of the Bankruptcy Code; (iii) a trustee shall be appointed in these cases; (iv) these cases shall be dismissed; or (v) if the NAS Baby Claimants fail to comply with any requirement of the NAS Baby Class Claims Procedures.

6. If this Stipulation is terminated, (a) the designation of the NAS Baby Class Claim as a Claim filed on behalf of the NAS Baby Class shall be rescinded and the NAS Baby Class Claim and any other Proof of Claim filed in connection herewith shall be treated as filed solely on behalf of the NAS Baby Claimants, and (b) the NAS Baby Claimants shall be relieved of any further obligations under the NAS Baby Class Claims Procedures.

7. This Stipulation constitutes the entire agreement between the Parties and supersedes all prior agreements and understandings, both written and oral, between the Parties with respect to the subject matter hereof and, except as otherwise expressly provided herein, is not intended to confer upon any other person any rights or remedies hereunder.

8. Except as expressly set forth in this Stipulation or the NAS Baby Class Claims Procedures, nothing contained herein shall be an admission or waiver of the substantive or procedural rights, remedies, claims, or defenses of any of the parties in these chapter 11 cases, whether at law or equity.

9. Each of the Parties shall bear its own attorneys' fees and costs with respect to the execution and delivery of this Stipulation and the NAS Baby Class Claims Procedures; *provided, however*, that the allowed attorneys' fees and costs of the Committee shall be paid pursuant to applicable provisions of the Bankruptcy Code and orders of the Court.

10. This Stipulation may be executed in counterparts, any of which may be transmitted by facsimile or electronic mail, and each of which shall be deemed an original and all of which together shall constitute one and the same instrument.

11. This Stipulation and the NAS Baby Class Claims Procedures may not be amended without the express written consent of all Parties hereto.

12. It is acknowledged that each Party has participated in and jointly consented to the drafting of this Stipulation and the NAS Baby Class Claims Procedures and that any claimed ambiguity shall not be construed for or against either Party on account of such drafting.

13. The Court shall retain jurisdiction over any and all disputes or other matters arising under or otherwise relating to this Stipulation.

Dated: December 4, 2019
Wilmington, Delaware

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EXHIBIT 1-A

Class Claim Procedures
NAS Monitoring Class Claim

1. The **NAS Monitoring Class** includes all NAS diagnosed children with a Claim for medical monitoring support against Insys.

2. No Distributions[1] will be made to the NAS Monitoring Class Representative (a trustee to be appointed pursuant to the Plan) on the NAS Monitoring Class Claim under the Plan, and instead, will be held by the Liquidating Trustee for the benefit of the NAS Monitoring Class, until an NAS Monitoring Allocation Plan has been approved by the Bankruptcy Court.

3. Within six months of the Effective Date of the Plan, the selected NAS Monitoring Class Representative will propose a plan based on expert analysis and empirical observation to allocate Distributions in support of the development and implementation of a national NAS children monitoring system (the "**NAS Monitoring Allocation Plan**" or "**NMAP**"). The NAS Monitoring Class Representative will file a motion and proposed order with the Bankruptcy Court seeking approval of the NAS Monitoring Allocation Plan, which will include provisions for the establishment of the NAS Escrow Account (described below).

4. If the NAS Monitoring Class Representative determines, after consultation with the Liquidating Trustee and after Bankruptcy Court approval of the NMAP, that implementation of the monitoring system would be uneconomical based on the amount of available Distributions, the NAS Monitoring Class Representative will establish an escrow account to hold Distributions (the "**NAS Escrow Account**") until such time as the funds available to the NAS Monitoring Class Representative are sufficient, in the NAS Monitoring Class Representative's sole discretion, to contribute to implementation of the national monitoring system. Upon the establishment of the NAS Escrow Account, the Liquidating Trustee will make Distributions under the Plan into the NAS Escrow Account.

5. The NAS Monitoring Class Representative will provide a status report to the Liquidating Trustee every 90 days from the date of the first payment into the NAS Escrow Account reflecting the status of the NAS Escrow Account until such time as the Distributions paid under the Plan into the NAS Escrow Account have been distributed in accordance with the NMAP.

[1] Capitalized terms used but not defined herein shall have the meanings ascribed to such terms in the *Second Amended Joint Chapter 11 Plan of Liquidation of Insys Therapeutics, Inc. and Its Affiliated Debtors* [Docket No. 928] (as may be amended or modified from time to time, the "**Plan**").

EXHIBIT B

DECLARATION OF DR. KANWALJEET S. ANAND

I am Dr. Kanwaljeet S. Anand, M.B.B.S., D.Phil., FAAP, FCCM, FRCPCH who files this declaration under penalty of perjury. I am a pediatrician specialized in the care of critically ill newborns and children. I serve as a fully tenured Professor of Pediatrics, Anesthesiology, Perioperative & Pain Medicine at Stanford University School of Medicine, and as Director of the Pain/Stress Neurobiology Laboratory at Children's Hospital Research Institute. For more than 30 years, I have conducted intensive research and study on the development of pain/stress in human newborns, their development during early childhood, and long-term outcomes. I have authored 311 scientific publications (125 in the last 10 years), edited 9 books, and received numerous professional awards. My true and correct Curriculum Vitae is attached. I am personally familiar with Opioid Use Disorder in adult females and Neonatal Abstinence Syndrome and have reviewed the materials referenced below.

The President of the United States had declared a national medical emergency caused by the Opioid Crisis in America[1]. The immediate effects of the Opioid Crisis, however, may be strikingly less consequential when compared to its effects on the individuals who were exposed to opioid drugs prenatally, many of whom were diagnosed with NAS. These children, through no fault of theirs, have been condemned to suffer from the short-term and long-term effects of opioid exposure from birth throughout their childhood, adolescence and into their adult lives. Though the current Opioid Crisis looms large on the thinking of social, medical, or government establishments, but its long-term impact is inestimable because of the pervasive and persistent effects of prenatal opioids on all aspects of an individual's development. Their cumulative burden of suffering, and the total impact of their exposures on all facets of our society is so huge and unparalleled in human history that this is truly the real emergency. Unless they are monitored/supported/treated NOW, the problems of these children will become intractable and unmanageable as they grow into adulthood, wiping away generations of human endeavor because of our short-sightedness. I offer the following statements for the Court's consideration:

Definitions

- Opioid Use Disorder (OUD) is defined in the DSM-5 as a problematic pattern of opioid use leading to clinically significant impairment or distress. OUD was previously classified as Opioid Abuse or Opioid Dependence in DSM-IV.
- OUD has also been referred to as "opioid addiction" in previous publications. Addiction is defined as a chronic, relapsing syndrome of psychological dependence and craving of a drug for its psychedelic, sedative, or euphoric effects; characterized by compulsion, loss of control, and continued use of a substance despite knowledge of its harmful effects[2].
- Infants and children are not "users" as defined under the DSM-5 criteria and are excluded from the class of persons suffering from OUD. Regardless, the birth mothers of children diagnosed with neonatal abstinence syndrome (NAS) would be included within the definition of OUD.
- Neonatal abstinence syndrome (NAS) or neonatal opioid withdrawal syndrome (NOWS) are terms used to denote a group of problems that occur in the children who were exposed to opioid or opiate drugs in the mother's womb. NAS is diagnosed clinically based on the clinical signs occurring in the 1 week after birth, characterized by neurologic hyperexcitability, gastrointestinal dysfunction, and autonomic instability. Most common neurologic signs include anxiety, agitation,

grimacing, insomnia, increased muscle tone/reflexes, exaggerated startle reflexes, high-pitched crying, tremors and abnormal movements, seizures; gastrointestinal symptoms include vomiting, diarrhea, poor sucking, dehydration; autonomic signs include elevated heart rate, respiratory rate, and blood pressure, fever, sweating, mottled skin, yawning, skin excoriation, cold extremities[2-5].

Notes: 1. Most clinicians diagnose NAS in children with modified Finnegan score of 8 or greater from two (2) consecutive assessments performed by a qualified healthcare practitioner with a minimum interval of 4 hours between the two consecutive NAS assessments[6-9]. Although the Finnegan NAS was criticized in various publications and alternatives were suggested, however, it is still the most widely used method for making a clinical diagnosis of NAS[10,11]. Simplified versions of the Finnegan NAS scale were developed and cross-validated against the original Finnegan score but did not show any significant improvement in psychometric properties[12-14]. Other methods for making the NAS diagnosis include the Rivers opiate withdrawal tool[15], the Lipsitz narcotic withdrawal score (cut-off score of 4 or more indicates NAS)[14], the neonatal narcotic withdrawal index (cut-off score of 5 or more indicates NAS)[16], and other less commonly used methods. Two recent studies have substantiated the validity of a clinical diagnosis for NAS coded within the patient's medical record at the time of hospital discharge[17,18]. A quality improvement (QI) initiative showed increases in the accuracy and consistency of Finnegan NAS scoring by nurses, but the effects of this training were short-lasting[19].

2. Although all children born to birth mothers suffering from OUD in pregnancy may or may not show signs/symptoms of NAS or NOWS, their brain development has been altered by repeated exposures to opioid drugs in the prenatal period. NAS signs/symptoms are the clinical manifestations resulting from sudden withdrawal of the prenatal opioid exposure, whereas the structural and functional alterations in their brain cells, connections, and architecture, as well as the brain damage from opioid-induced apoptosis (programmed cell death) occurs long before a child is born. These changes in brain development are permanent and will affect these children throughout their entire lifespan (see below). Therefore, we need to establish a class of individuals who were exposed to opioid drugs prenatally, particularly those who were diagnosed with NAS/NOWS after birth.

3. For the purposes of monitoring and surveillance, therefore, the following objective criteria will identify children with NAS and at risk for long-term neurodevelopmental consequences of prenatal opioid exposures:

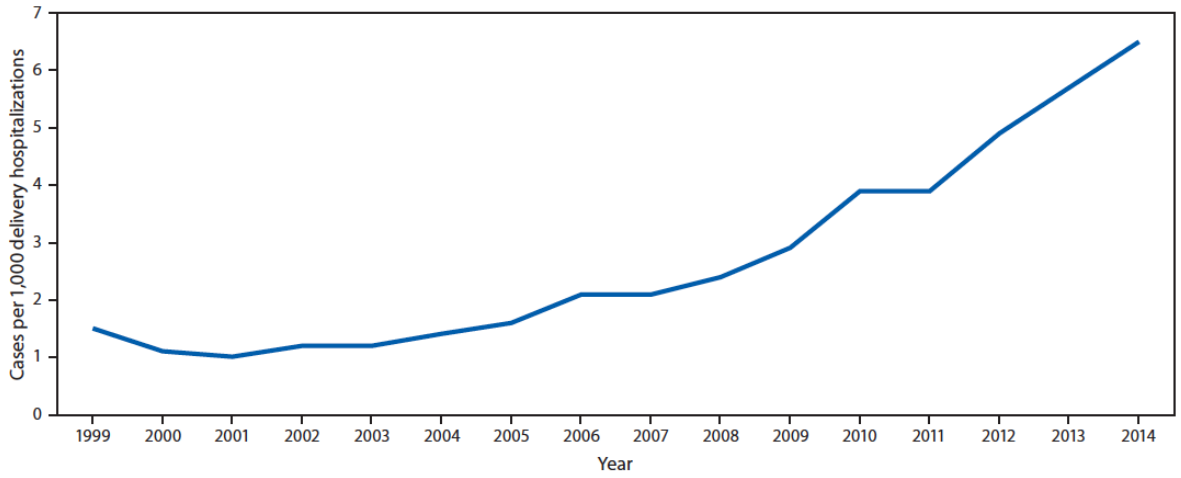
a) Diagnosis of NAS or NOWS documented in the child's medical record, for example, using the diagnostic codes of: P96.1/P04.49 (ICD-10 CM), 779.5/760.72 (ICD-9 CM)[18]; and/or
b) Monitoring of NAS/NOWS score(s) after birth, meeting the diagnostic criteria as defined above; and/or
c) Postnatal weaning of opioid drugs (morphine, methadone, buprenorphine, or other opioids); and/or
d) Children who are already listed in a national registry or other registries established for NAS[20]; and/or
e) Toxicology screen of (a) maternal blood, urine, or hair analysis, (b) umbilical cord blood, (c) baby's meconeum testing positive for opioids (excluding mothers who were prescribed opioids after the onset of, or for the purpose of treating labor pains, or for treating procedural pain).

The numbers of babies exposed to prenatal opioids annually

1) Based on trend analyses for birth mothers suffering from OUD in pregnancy, approximately 36,000 babies are likely to be born with prenatal opioid exposures in 2018[21] (projected using the CDC birth rate data)[22-24]. CDC data show that the documented rate for birth mother OUD was 6.5 per 1,000 delivery hospitalizations in 2014 (MMWR, August 2018[21]). This is a conservative estimate, since it does not include babies delivered at home, at maternity clinics, or birthing centers. Epidemiological studies show that rates of birth mother OUD may be higher among women who use non-hospital birthing centers or prefer delivering their baby at home[21,25-27].

2) Using data from 1999 to 2014[21], the National Average Annual increase in opioid exposed birth rates for mothers suffering from OUD was 0.39 per 1,000 delivery hospitalizations per year. This estimate averages the increases in birth mother OUD rates over 16 years of collected data, although the rate of increase was much greater in the last 5 years of data collection (Figure 1).

FIGURE 1. National prevalence of opioid use disorder per 1,000 delivery hospitalizations* — National Inpatient Sample (NIS),† Healthcare Cost and Utilization Project (HCUP), United States, 1999–2014



Even using this conservative yearly rate increase (3.9%) will give us prenatal opioid exposure rates increasing up to 8.45 per 1,000 delivery hospitalizations in 2019. However, if we project the prenatal opioid exposure rate increases from the past 5 years, National Average increases show an increased rate of 7.2% or 0.72 per 1,000 delivery hospitalizations per year. This will give us prenatal opioid exposure rates increasing to 10.1 per 1,000 delivery hospitalizations in 2019. These data are listed in **Table 1** on the next page. Table 1 also includes the "corrected" prenatal opioid exposure rates after adjusting for: (1) women undergoing detox before the baby's birth, whose babies may not show signs of NAS; and (2) those women who do not deliver in a hospital (previous studies have reported higher OUD rates among these women).

Annual growth rate of individuals at risk for NAS

3) More than half (60-75%) of the individuals born to birth mothers with OUD in pregnancy are expected to be diagnosed with NAS as defined above[21,28-36]. Those diagnosed with NAS are more likely than non-NAS individuals to have more significant exposures to prenatal opioids and to have developed subcellular and other physiological changes as a result of such exposures. CDC states that individuals at risk for NAS are **"clearly underestimated and under-reported"** but

the data available from 36 states in 2015 showed approximate increases of 7.2% occurring in each year between 2011 and 2015[21,26,27,37,38].

Table 1: Numbers of Individuals at risk for NAS: Trend analyses from 2014 to 2019

	National Average Increase 0.39/year (**1999-2014** data)			National Average Increase 0.72/year (**2011-2014** data)			Estimates including babies who detox *in utero* and those born in non-hospital settings		
	OUD rate/1000 hospital deliveries	Number of live-births: CDC data	Newborns with prenatal opioid exposures	OUD rate/1000 hospital deliveries	Number of live-births: CDC data	Newborns with prenatal opioid exposures	Corrected OUD rates/1000 live births	Number of live-births: CDC data	Newborns with prenatal opioid exposures
2014	6.5	3,988,076	25,922	6.5	3,988,076	25,922	7.5	3,988,076	29,911
2015	6.89	3,978,497	27,412	7.22	3,978,497	28,725	8.5	3,978,497	33,817
2016	7.28	3,945,875	28,726	7.94	3,945,875	31,330	9.4	3,945,875	37,091
2017	7.67	3,853,472	29,556	8.66	3,853,472	33,371	10.3	3,853,472	39,691
2018*	8.06	3,776,403	30,438	9.38	3,776,403	35,423	11.1	3,776,403	41,918
2019*	8.45	3,738,639	31,591	10.1	3,738,639	37,760	11.9	3,738,639	44,490

*2018 Number of Live-births estimated with a 2% decrease in births from 2017; *2019 Number of Live-births estimated with a 1% decrease in births from 2018

Constellation of clinical conditions associated with NAS

4) Opioids are proven hazardous substances for prenatal human development. Thus, NAS is associated with premature birth, low birth weight, intrauterine growth retardation (IUGR), perinatal or neonatal mortality, increased birth defects, delayed cognitive development, long-term behavioral problems, ADHD, auditory deficits, speech delay, swallowing difficulty, gastro-esophageal reflux disease (GERD), digestive or gastrointestinal motility disorders, delayed feeding, failure to thrive, congenital neurological defects, and congenital heart defects[39-45].

Time periods of interventions to achieve the best outcomes

5) For most of the conditions listed above, the best possible outcomes can only be achieved with proper management of NAS before hospital discharge, coupled with increased monitoring and surveillance, as well as active multi-disciplinary interventions that are initiated just after birth and continued for the child's entire childhood and adolescence (up to 18 years of age)[30,39,46-56].

Evidence suggesting that prenatal opioid exposure damages DNA

6) Huge amounts of published data substantiate the findings that prenatal opioid exposures alter genetic regulation and DNA structure, although many of these studies were performed in animal models[57]. Almost 40 years ago, however, leading researchers discovered that prenatal opioid

exposure damages human DNA and/or prevents DNA repair occurring from other causes of DNA damage (e.g. UV light)[58]. Since then, accumulating data have shown the progressive and persistent effects of repetitive prenatal opioid exposure on DNA fragmentation occurring in the developing human brain and in peripheral blood cells[58-71]. More recently, several studies also documented the epigenetic effects of opioid addiction, capable of intergenerational and transgenerational transmission to the offspring of opioid addicts[72-80]. Although pregnant women were excluded from some of these studies, the underlying mechanisms are the same and will have extensive effects on the massive amounts of DNA synthesis occurring during prenatal human development[66,81].

Consequent to the opioid effects on human DNA cited above, a large number of studies have found a higher incidence of birth defects in the babies exposed to maternal opioids *in utero*[45]. Seventeen (17) studies found opioid exposure linked with facial/oral defects (e.g., cleft lip, cleft palate, or others), heart defects (e.g., ventricular septal defects, atrial septal defects, hypoplastic left heart syndrome, pulmonary valve stenosis, conoventricular septal defects), limb deformities (e.g., clubfoot), visceral organ defects (e.g., gastroschisis), or neural tube defects (e.g., spina bifida)[40,41,43-45]. Most of these conditions require multiple surgical operations and long-term medical care to support the optimal development of these severely affected children[43,82].

Long-term cognitive and behavioral outcomes of individuals diagnosed with NAS

7) Brain Development: Opioids have drastic and sustained effects on brain development in the fetal and postnatal periods, affecting the brain's size, architecture, networks and connections between brain cells, neurochemical and other functions of each cell, as well as the brain DNA's structure, its expression and regulation. Thus, prenatal opioid exposures have robust and long-term effects on the cognitive and behavioral outcomes of the individuals diagnosed with NAS[82]. Opioids affect brain development by disrupting oligodendrocyte development, altering the temporal sequencing and quality of nerve fiber myelination[83], decreasing the growth of nerve cell dendrites[84,85] and their branching pattern complexity of pyramidal neurons in the cerebral cortex[40], and by suppressing cell proliferation and neuronal migration to the cortical plate[86]. These effects may reduce regional brain volumes in the basal ganglia[87] and other brain areas[87-90], with lower developmental potential.

8) Brain Growth: A large number of studies have reported lower birth weights and smaller head circumferences in opioid-exposed babies with relatively increased risks in those exposed [20,36,87,91-99]. A controlled comparison showed that reduced fetal head and body growth in infants of opioid-dependent mothers were not explained by gestational age, cigarette smoking, area deprivation, infant gender, maternal age or parity[100]. Given the limited maternal/environmental effects on head circumference, it is likely that the robust effects of opioid exposure on head circumference occur by reducing brain growth[82,101]. This was confirmed in a pilot study of 16 infants, where volumetric MRI scans showed smaller whole brain volumes and basal ganglia volumes compared to age-matched population means[87]. In another follow-up MRI study that included 38 youths in the opioid-exposed group and 44 youths in the non-exposed group (aged 17 to 22 years), the drug-exposed group displayed smaller brain volumes, smaller surface areas of the cerebral cortex, and thinner cortical mantles than unexposed youth[88].

9) Functional Effects: The consequences of this impaired brain growth are also pervasive, with altered dyadic interactions between mothers and infants[102], impaired early development in all domains of the Griffith's Mental Development Scales[103], impaired visual acuity and visuomotor

functions (eye-hand coordination)[101,103,104], impaired language-related cognitive skills and executive functions[105,106], with inattention, hyperactivity, impulsivity, aggression, ADHD, other social and behavioral problems persisting into adolescence and even adulthood in those born to opioid-dependent mothers during pregnancy[88,91,107-109]. Baldacchino et al. identified 200 follow-up studies of opioid exposures during pregnancy, but only 8 studies met inclusion criteria with 4 studies in infancy, 3 assessing preschool children, and 1 on school children[110,111]. All these were case-control studies conducted within urbanized, low socioeconomic communities, with mothers exposed to either heroin or methadone. Five studies had data usable for meta-analysis, with a total of 218 opioid-exposed and 205 non-exposed children. In all outcomes opioid-exposed children had lower scores as compared to controls[110].

10) Neurodevelopmental Consequences: Differences in neurodevelopment between children with and without exposure to prenatal opioids are related to the age at which they were assessed, with milder differences occurring at birth, greater differences during infancy and early childhood but widening gaps noted during school age and adolescence. Individuals with NAS at birth had impaired behavioral regulation, greater excitability and arousal, and poorer quality of their movements[112-121]. Among infants and toddlers, NAS was associated with impaired mental and language development as well as poorer neuromotor and psychomotor development before 24 months of age[122]. Because of the very limited roles for cognitive or executive functions in early childhood, studies performed in the younger age groups showed minimal differences in cognitive or executive functions with and without NAS[123,124] (e.g., every infant is likely to fail an algebra test). In contrast, the Bayley Scales of Infant Development revealed more prominent neurodevelopment deficits, with greater vulnerability among boys than in girls[125-127]. Assessment in later childhood revealed differences in IQ, motor performance[128-131], language performance[132], lower IQ scores, behavior and attention problems compared with unexposed children at 8.5 years of age[107,108]. Children exposed to methadone prenatally also had elevated levels of aggression, fear, and anxiety[91,130,133]. Even after controlling for their sociodemographic factors and birth mother's medical history, elevated symptoms of ADHD occurred in children who were exposed to prenatal opioids compared with children not exposed to opioids *in utero* [91,130,134].

A recent systematic review and meta-analysis of cohort studies of 1,455 children from birth to 18 years found that prenatal opioid exposures negatively impacted neurocognitive outcomes and physical/motor development from age 6 months onwards, and this association persisted until adolescence[135]. The study could not differentiate between the contributions of prenatal opioid exposure vs. opioid treatment for NAS after birth and recommended that all NAS children should receive long-term monitoring, with social, emotional and educational support or intervention[135]. The long-term effects of prenatal opioids on cognition tended to increase over time, even in those children who were adopted or placed in foster care, thus being exposed to minimal postnatal risk factors[107]. NAS children discharged home with their birth mother, despite a longer hospital stay, had a higher likelihood of being referred for early intervention services (81%) compared to those placed in foster care (66%)[136].

11) Executive Functions: Executive functions are thinking skills that help us with the information processing, reasoning, planning, problem-solving, for coping with stress, regulating our emotions and managing our lives. As a child progresses through school, the executive functions assume greater importance in their academic success, goal setting, and employability[137]. Children exposed to prenatal opioids have difficulties with information processing[138], poorer performance on a

vigilance task[139], lower overall executive functioning[105], significantly lower visual acuity[101], impaired visual-motor and perceptual performances, and fewer goal-directed eye movements[140-142]. Children with NAS were far more likely to have developmental delays and lower IQ[143], 2.3 times more likely to be hospitalized for neuropsychiatric disorders[144], 4.5 times more likely to be hospitalized for child abuse[144] and die during hospitalization[144], perform poorly on educational testing[145], and show cognitive disabilities requiring extra classroom therapies and services[146]. CDC compared 1815 children with NAS and 5441 children without NAS (age 3-8 years). Children with NAS were more likely referred for disability evaluation (19.3% vs. 13.7%), have a learning disability (15.6% vs. 11.7%) and require classroom therapies (15.3% vs. 11.4%). These differences remained significant even after controlling for maternal smoking, maternal education, birth weight, gestational age, and/or NICU admission[146]. Children with NAS had lower scores on standardized testing in grade 3; by grade 7, children with NAS were scoring lower than other children in grade 5 and showing progressively greater deficits[145]. The increasingly complex cognitive processing and executive functioning required within a competitive high school environment place these children with NAS at progressively greater disadvantage and much higher likelihood of adverse outcomes, thus widening the gap between those with and without NAS.

12) Neuropsychiatric outcomes: Although Uebel et al. (2015) had found that more children with NAS were hospitalized with neuropsychiatric disorders (adjustment, conduct, anxiety, emotional, or speech disorders), three recent studies have highlighted the very high prevalence and distribution of mental health conditions among individuals with prenatal opioids. Using a Medicaid database, Sherman et al. (2019) found that half of all children with NAS were diagnosed with mental disorder before age 5, compared with 30% of all other births. Children with NAS were more likely to have conduct disturbances (2.7-fold), hyperkinetic syndromes (2.6-fold), adjustment difficulties (2.5-fold), stress/anxiety disorders (1.5-fold), emotional problems (1.9-fold), childhood-onset psychoses (1.7-fold), intellectual disabilities (2.3-fold), specific developmental delays (1.7-fold)[147]. Mental health conditions were 1.6-fold more prevalent in children with a history of NAS than the opioid-exposed children without a history of NAS, and 1.4-fold higher among children with Medicaid vs. commercial health insurance (Table 2 from Conner et al., 2019)[148]. From a longitudinally followed youth cohort (17-22 years) with prenatal opioid exposures (± other drugs) who were adopted/fostered before 1 year of age, Nygaard et al. (2019) found **2- to 8-fold higher lifetime risk of mental disorders** compared to matched controls[149]. These risks mainly included

TABLE 2 Diagnoses of mental health conditions in children with and children without neonatal abstinence syndrome (NAS), by Medicaid or commercial insurance coverage

	Commercial insurance (N=1,405,712)				Medicaid[a] (N=270,772)			
	NAS (N=190)		No NAS (N=1,405,522)		NAS (N=1,046)		No NAS (N=269,726)	
Diagnosis (*ICD-9* code)	N	%	N	%	N	%	N	%
Any mental health condition/diagnosis	68	35.8	313,021	22.3	511	48.9	81,814	30.3
Specific delays in development (315)	48	25.3	115,785	8.2	327	31.3	49,591	18.4
Disturbance of conduct (312)	11	5.8	37,120	2.6	113	10.8	10,879	4.0
Hyperkinetic syndrome of childhood (314)	13	6.8	102,770	7.3	94	9.0	9,372	3.5
Adjustment reaction (309)	9	4.7	63,295	4.5	75	7.2	7,799	2.9
Acute reaction to stress (308)	2	1.1	6,995	.5	49	4.7	8,123	3.0
Neurotic disorders (300)	9	4.7	60,749	4.3	43	4.1	7,365	2.7
Special symptoms or syndromes (307)	11	5.8	58,585	4.2	41	3.9	9,672	3.6
Disturbance of emotion specific to childhood and adolescence (313)	2	1.1	23,686	1.7	39	3.7	5,350	2.0
Intellectual disabilities (317–319)	1	.5	2,596	.2	37	3.5	4,074	1.5
Psychoses with origin specific to childhood (299)	8	4.2	26,860	1.9	32	3.1	4,752	1.8

[a] Source: Sherman et al., 2019 (2). Adapted by permission from American Psychiatric Association Publishing.

major depression, alcohol abuse, ADHD, and **aggressive behaviors** even after controlling for age, gender, and caregivers' education. These children not only engaged in sex at younger ages and had **more sexual partners** compared to controls, but also experienced **suicidality** (28.8%), **psychoses** (17.7%), or **antisocial personality disorder** (15.6%) more often than their peers[149].

Such bleak outcomes portend a future tsunami of neurocognitive and neuropsychiatric disorders among the children and youth with NAS. The Opioid Crisis has increased over the past 20 years; therefore, multiple generations of such children and youth have been affected. While we continue to argue about priorities and preferences, these children are growing up – and every day that passes without the medical monitoring or supportive services being offered to these children, it makes their problems more and more intractable, imposing on them poorer outcomes and greater societal disadvantages.

Urgent need for more scientific investigations of individuals with NAS

Despite the recent flurry of scientific publications on this topic, there are numerous unanswered questions about the epidemiology, risk factors, diagnoses, management, and responses to therapy in the children with NAS. Therefore, there is an urgent need for a court-appointed Science Panel with the imperative to document the long-term outcomes of children exposed to prenatal opioids, through multiple, well-designed, large studies that prospectively enroll adult women with OUD and ensure good retention rates, to longitudinally follow their children with NAS at least until 18 years of age. All these children will require detailed neurocognitive and neuropsychiatric testing, as well as functional monitoring. Such tests are not available during routine doctor visits or other healthcare settings. To be explicit, these needs exist well-above and beyond the routine pediatric care and/or schooling required for non-opioid exposed children. These needs are not currently covered by Medicaid, or any private health insurance or any kind of Special-Ed funding. To obtain such data and to ensure that appropriate therapies and social services are offered, these children require detailed medical monitoring and surveillance through a well-coordinated, standardized, multidisciplinary, and nationally implemented protocol as described below. The results of such monitoring and surveillance must be regularly evaluated by the court-appointed Science Panel, so that accumulating data and scientific insights can be applied to the ongoing care of these children. To inform members of the Science Panel, they must be given access to all scientific and medical studies, data, experiments, white papers, research forms, or other materials related to the synthetic opioids, regardless of whether such materials had ever been provided to the FDA or whether they were protected assert trade secret protection.

Protocol for monitoring/surveillance of children diagnosed with NAS

1) Biological variability is based on genetic and epigenetic mechanisms, or factors related to the prenatal opioid exposure that manifested NAS (specific drugs, dosage, period(s) of pregnancy affected, detox or treatment effects, exposures to smoking, alcohol, or other drugs), as well as the postnatal treatments for NAS. All these will influence the child's long-term neurodevelopmental consequences resulting from NAS. Individual differences occurring between humans are difficult to determine specifically, but a common medical monitoring program is absolutely essential for all NAS victims because they are all at high-risk for common detrimental outcomes, associated with 'hidden' or latent conditions and disorders that can be ameliorated through medical monitoring, scheduled assessments, surveillance procedures and appropriate therapies. The proposed monitoring is different from that normally recommended in the absence of opioid exposures and

there is immense clinical value in the early detection and diagnosis of long-term opioid effects. If our societal goal is to achieve the maximal developmental outcomes for all children, then uniform and robust program will be necessary. Although some children might ultimately benefit more than others, however, that can be attributed to a biological variability in response to therapy, other psychosocial factors, or presently unknown factors that require further scientific investigation.

2) Children with NAS are at higher risk for a variety of adverse outcomes as noted above. Therefore, they are worthy of a more structured and specialized program of monitoring and surveillance with scheduled extra assessments, for at least two reasons. First, their families/caregivers want to know if their child is healthy and growing and developing normally, and they want to know about the health or other problems likely to be encountered in the future. Special concerns often arise at childhood or social transition points, such as entering childcare or changing school levels, thus requiring careful guidance and advice. Second, most of their developmental problems can be ameliorated or prevented if detected early – identification of high-risk groups for targeted interventions can be both cost-effective and efficient. Multidisciplinary advice from Doyle et al. (2014)[150] was used to design the monitoring protocol as outlined below.

3) If these periodic diagnostic medical exams identify a particular deficit or disability, the child's caregivers must be provided access to the specific resources and treatment(s) that they will need to overcome the long-term impacts of NAS. Additionally, caring for a victim of NAS is difficult, associated with increased risks for repeated hospitalizations of the child. An educational program aimed at increasing the understanding of NAS in parents and other caregivers is recommended, including access (or referral) to resources for both the caregiver and the child.

4) Barriers for implementing standardized monitoring protocols must be anticipated and addressed. These may include providing funding for transportation to scheduled assessments or making the transport arrangements, providing token compensation to participants, facilitating access by offering home visits or assessments at a location convenient for the parent/caregiver, consideration for living situation, and other barriers.

5) Most of these assessments are required annually, unless specified otherwise. Certain specialist assessments may be required only once (e.g., cardiology evaluation to rule-out congenital heart disease), or to be determined by the results of the previous testing – more frequent assessments will be required for the NAS children with abnormal/atypical results.

6) The data gained from these assessments must be deidentified, aggregated and securely stored in a state-level database, with query access available to researchers, practitioners, social or healthcare agencies, advocacy groups and others.

In conclusion, implementation of the studies referenced herein as well as the long-term care and treatment of these babies is essential to the resolution of the Opioid Crisis and its impact on our society. This report is based upon the information available at the time it was prepared. With the recent increase in NAS cases, the scientific understanding of NAS and the outcomes of NAS victims continues to evolve. And yet, much work remains to be done, which is the goal of implementing a long-term Court-appointed Science Panel – to study the results of the monitoring and surveillance and to recommend interventions as needs arise. With the Court's permission, I

would like to reserve the right to update this report in order to reflect the accumulating scientific and medical evidence as necessary.

I certify under penalty of perjury that the foregoing is true and correct.

Executed on December 8, 2019.

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References:

1. Terplan M. Beyond the Treatment Box: Perspectives on the Federal Response to Opioid Use, Pregnancy, and Neonatal Abstinence Syndrome. J Addict Med 2017;11:176-7.
2. Anand KJS, Willson DF, Berger J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics 2010;125:e1208-25.
3. Anand KJS, Arnold JH. Opioid tolerance and dependence in infants and children. Crit Care Med 1994;22:334-42.
4. Suresh S, Anand KJS. Opioid tolerance in neonates: mechanisms, diagnosis, assessment, and management. Semin Perinatol 1998;22:425-33.
5. Suresh S, Anand KJS. Opioid tolerance in neonates: a state-of-the-art review. Paediatr Anaesth 2001;11:511-21.
6. Finnegan LP, Connaughton JF, Jr., Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis 1975;2:141-58.
7. Finnegan LP, Kron RE, Connaughton JF, Emich JP. Assessment and treatment of abstinence in the infant of the drug-dependent mother. Int J Clin Pharmacol Biopharm 1975;12:19-32.
8. Lifshitz M, Gavrilov V, Galil A, Landau D. A four year survey of neonatal narcotic withdrawal: evaluation and treatment. Isr Med Assoc J 2001;3:17-20.
9. Zimmermann-Baer U, Notzli U, Rentsch K, Bucher HU. Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5-6 in non-addicted infants. Addiction 2010;105:524-8.
10. Kocherlakota P. Neonatal abstinence syndrome. Pediatrics 2014;134:e547-61.
11. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. N Engl J Med 2015;372:2118-26.
12. Maguire D, Cline GJ, Parnell L, Tai CY. Validation of the Finnegan neonatal abstinence syndrome tool-short form. Adv Neonatal Care 2013;13:430-7.
13. Gomez Pomar E, Finnegan LP, Devlin L, et al. Simplification of the Finnegan Neonatal Abstinence Scoring System: retrospective study of two institutions in the USA. BMJ Open 2017;7:e016176.
14. Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants. A pragmatic evaluation of its efficacy. Clin Pediatr (Phila) 1975;14:592-4.
15. Rivers RP. Neonatal opiate withdrawal. Arch Dis Child 1986;61:1236-9.
16. Green M, Suffet F. The Neonatal Narcotic Withdrawal Index: a device for the improvement of care in the abstinence syndrome. Am J Drug Alcohol Abuse 1981;8:203-13.
17. Yam P, Lok L, Eastwood J, et al. Validation of hospital discharge coding for neonatal abstinence syndrome. Acta Paediatr 2019;108:1786-92.
18. Maalouf FI, Cooper WO, Stratton SM, et al. Positive Predictive Value of Administrative Data for Neonatal Abstinence Syndrome. Pediatrics 2019;143.
19. Timpson W, Killoran C, Maranda L, Picarillo A, Bloch-Salisbury E. A Quality Improvement Initiative to Increase Scoring Consistency and Accuracy of the Finnegan Tool: Challenges in Obtaining Reliable Assessments of Drug Withdrawal in Neonatal Abstinence Syndrome. Adv Neonatal Care 2018;18:70-8.

20. Nechanska B, Mravcik V, Skurtveit S, et al. Neonatal outcomes after fetal exposure to methadone and buprenorphine: national registry studies from the Czech Republic and Norway. Addiction 2018;113:1286-94.
21. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid Use Disorder Documented at Delivery Hospitalization - United States, 1999-2014. MMWR Morb Mortal Wkly Rep 2018;67:845-9.
22. Martin JA, Hamilton BE, Osterman MJ, Driscoll AK, Mathews TJ. Births: Final Data for 2015. Natl Vital Stat Rep 2017;66:1.
23. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final Data for 2016. Natl Vital Stat Rep 2018;67:1-55.
24. Hamilton BE, Martin JA, Osterman MJ, Driscoll AK, Rossen LM. Births: Provisional Data for 2017. Washington, DC: Centers for Disease Control & Prevention, U.S. Department of Health and Human Services; 2018.
25. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA 2012;307:1934-40.
26. Atwell KA, Weiss HB, Gibson C, Miller R, Corden TE. Neonatal Abstinence Syndrome and Maternal Substance Use in Wisconsin, 2009-2014. WMJ 2016;115:287-94.
27. Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of Neonatal Abstinence Syndrome - 28 States, 1999-2013. MMWR Morb Mortal Wkly Rep 2016;65:799-802.
28. Ko JY, Wolicki S, Barfield WD, et al. CDC Grand Rounds: Public Health Strategies to Prevent Neonatal Abstinence Syndrome. MMWR Morb Mortal Wkly Rep 2017;66:242-5.
29. Reddy UM, Davis JM, Ren Z, Greene MF, Opioid Use in Pregnancy NAS, Childhood Outcomes Workshop Invited S. Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes: Executive Summary of a Joint Workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. Obstet Gynecol 2017;130:10-28.
30. Kraft WK, Stover MW, Davis JM. Neonatal abstinence syndrome: Pharmacologic strategies for the mother and infant. Semin Perinatol 2016;40:203-12.
31. Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol 2015;35:650-5.
32. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. Pediatrics 2015;135:842-50.
33. Brandt L, Finnegan LP. Neonatal abstinence syndrome: where are we, and where do we go from here? Curr Opin Psychiatry 2017;30:268-74.
34. Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag 2009;5:47-55.
35. McQueen KA, Murphy-Oikonen J, Desaulniers L. Maternal Substance Use and Neonatal Abstinence Syndrome: A Descriptive Study. Matern Child Health J 2015;19:1756-65.
36. Hytinantti T, Kahila H, Renlund M, Jarvenpaa AL, Halmesmaki E, Kivitie-Kallio S. Neonatal outcome of 58 infants exposed to maternal buprenorphine in utero. Acta Paediatr 2008;97:1040-4.
37. Lind JN, Petersen EE, Lederer PA, et al. Infant and maternal characteristics in neonatal abstinence syndrome--selected hospitals in Florida, 2010-2011. MMWR Morb Mortal Wkly Rep 2015;64:213-6.
38. Okoroh EM, Gee RE, Jiang B, McNeil MB, Hardy-Decuir BA, Zapata AL. Neonatal Abstinence Syndrome: Trend and Expenditure in Louisiana Medicaid, 2003-2013. Matern Child Health J 2017;21:1479-87.
39. Wolff K, Perez-Montejano R. Opioid neonatal abstinence syndrome: controversies and implications for practice. Curr Drug Abuse Rev 2014;7:44-58.
40. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:314 e1-11.
41. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol 2013;122:838-44.
42. Dawson AL, Razzaghi H, Arth A, et al. Maternal exposures in the National Birth Defects Prevention Study: Time trends of selected exposures. Birth Defects Res A Clin Mol Teratol 2015;103:703-12.
43. McCarthy M. Opioids are commonly prescribed to women of reproductive age despite birth defect risk, US CDC study shows. BMJ 2015;350:h456.
44. Interrante JD, Ailes EC, Lind JN, et al. Risk comparison for prenatal use of analgesics and selected birth defects, National Birth Defects Prevention Study 1997-2011. Ann Epidemiol 2017;27:645-53 e2.
45. Lind JN, Interrante JD, Ailes EC, et al. Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review. Pediatrics 2017;139.

46. Ballard JL. Treatment of neonatal abstinence syndrome with breast milk containing methadone. J Perinat Neonatal Nurs 2002;15:76-85.
47. Bell SG. Buprenorphine: a newer drug for treating neonatal abstinence syndrome. Neonatal Netw 2012;31:178-83.
48. Kraft WK, van den Anker JN. Pharmacologic management of the opioid neonatal abstinence syndrome. Pediatr Clin North Am 2012;59:1147-65.
49. Bagley SM, Wachman EM, Holland E, Brogly SB. Review of the assessment and management of neonatal abstinence syndrome. Addict Sci Clin Pract 2014;9:19.
50. Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US children's hospitals, 2004-2011. J Perinatol 2014;34:867-72.
51. McPherson C. Pharmacotherapy for Neonatal Abstinence Syndrome: Choosing the Right Opioid or No Opioid at All. Neonatal Netw 2016;35:314-20.
52. Grossman MR, Berkwitt AK, Osborn RR, et al. An Initiative to Improve the Quality of Care of Infants With Neonatal Abstinence Syndrome. Pediatrics 2017;139.
53. Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome. N Engl J Med 2017;376:2341-8.
54. Kraft WK, Adeniyi-Jones SC, Ehrlich ME. Buprenorphine for the Neonatal Abstinence Syndrome. N Engl J Med 2017;377:997-8.
55. Pryor JR, Maalouf FI, Krans EE, Schumacher RE, Cooper WO, Patrick SW. The opioid epidemic and neonatal abstinence syndrome in the USA: a review of the continuum of care. Arch Dis Child Fetal Neonatal Ed 2017;102:F183-F7.
56. Gadomski A, Riley M, Ramiza K, et al. Treating Neonatal Abstinence Syndrome in a Rural Hospital: Lessons Learned. Acad Pediatr 2018.
57. Jimenez-Gonzalez A, Garcia-Concejo A, Leon-Lobera F, Rodriguez RE. Morphine delays neural stem cells differentiation by facilitating Nestin overexpression. Biochim Biophys Acta 2018;1862:474-84.
58. Madden JJ, Falek A, Shafer DA, Glick JH. Effects of opiates and demographic factors on DNA repair synthesis in human leukocytes. Proc Natl Acad Sci U S A 1979;76:5769-73.
59. McLaughlin P, Mactier H, Gillis C, et al. Increased DNA Methylation of ABCB1, CYP2D6, and OPRM1 Genes in Newborn Infants of Methadone-Maintained Opioid-Dependent Mothers. J Pediatr 2017;190:180-4 e1.
60. Drobnis EZ, Nangia AK. Pain Medications and Male Reproduction. Adv Exp Med Biol 2017;1034:39-57.
61. Abo-Elnazar S, Moaaz M, Ghoneim H, Molokhia T, El-Korany W. Th17/Treg imbalance in opioids and cannabinoids addiction: relationship to NF-kappaB activation in CD4+ T cells. Egypt J Immunol 2014;21:33-47.
62. Feng YM, Jia YF, Su LY, et al. Decreased mitochondrial DNA copy number in the hippocampus and peripheral blood during opiate addiction is mediated by autophagy and can be salvaged by melatonin. Autophagy 2013;9:1395-406.
63. Perez-Alvarez S, Iglesias-Guimarais V, Solesio ME, et al. Methadone induces CAD degradation and AIF-mediated necrotic-like cell death in neuroblastoma cells. Pharmacol Res 2011;63:352-60.
64. Hu S, Sheng WS, Lokensgard JR, Peterson PK. Morphine induces apoptosis of human microglia and neurons. Neuropharmacology 2002;42:829-36.
65. Zagon IS, Verderame MF, Allen SS, McLaughlin PJ. Cloning, sequencing, chromosomal location, and function of cDNAs encoding an opioid growth factor receptor (OGFr) in humans. Brain Res 2000;856:75-83.
66. Zagon IS, Wu Y, McLaughlin PJ. Opioid growth factor and organ development in rat and human embryos. Brain Res 1999;839:313-22.
67. Madden JJ, Falek A. The use of nonneuronal cells as an in vitro model system for studying the genetic component of cellular response to opiates and other drugs of abuse. J Addict Dis 1991;10:229-38.
68. Falek A, Donahoe RM, Madden JJ, Shafer DA. Opiates as immunosuppressive and genotoxic agents. Adv Exp Med Biol 1991;288:189-201.
69. Shafer DA, Falek A, Donahoe RM, Madden JJ. Biogenetic effects of opiates. Int J Addict 1990;25:1-18.
70. Falek A, Madden JJ, Shafer DA, Donahoe RM. Individual differences in opiate-induced alterations at the cytogenetic, DNA repair, and immunologic levels: opportunity for genetic assessment. NIDA Res Monogr 1986;66:11-24.
71. Shafer DA, Falek A, Madden JJ, et al. Parallel increases in sister-chromatid exchanges at base level and with UV treatment in human opiate users. Mutat Res 1983;109:73-82.
72. McCarthy JJ, Leamon MH, Finnegan LP, Fassbender C. Opioid dependence and pregnancy: minimizing stress on the fetal brain. Am J Obstet Gynecol 2017;216:226-31.
73. Wachman EM, Hayes MJ, Lester BM, et al. Epigenetic variation in the mu-opioid receptor gene in infants with neonatal abstinence syndrome. J Pediatr 2014;165:472-8.
74. Hurd YL, O'Brien CP. Molecular Genetics and New Medication Strategies for Opioid Addiction. Am J Psychiatry 2018:appiajp201818030352.

75. Goldberg LR, Gould TJ. Multigenerational and transgenerational effects of paternal exposure to drugs of abuse on behavioral and neural function. Eur J Neurosci 2018.
76. Crist RC, Reiner BC, Berrettini WH. A review of opioid addiction genetics. Curr Opin Psychol 2018;27:31-5.
77. Marie-Claire C, Jourdaine C, Lepine JP, Bellivier F, Bloch V, Vorspan F. Pharmacoepigenomics of opiates and methadone maintenance treatment: current data and perspectives. Pharmacogenomics 2017;18:1359-72.
78. Marie-Claire C, Crettol S, Cagnard N, et al. Variability of response to methadone: genome-wide DNA methylation analysis in two independent cohorts. Epigenomics 2016;8:181-95.
79. Andersen AM, Dogan MV, Beach SR, Philibert RA. Current and Future Prospects for Epigenetic Biomarkers of Substance Use Disorders. Genes (Basel) 2015;6:991-1022.
80. Nielsen DA, Utrankar A, Reyes JA, Simons DD, Kosten TR. Epigenetics of drug abuse: predisposition or response. Pharmacogenomics 2012;13:1149-60.
81. Oei JL, Xu HX, Abdel-Latif ME, et al. Dopamine D2 receptor gene polymorphisms in newborn infants of drug-using women. Arch Dis Child Fetal Neonatal Ed 2012;97:F193-8.
82. Anand KJS, Campbell-Yeo M. Consequences of prenatal opioid use for newborns. Acta Paediatr 2015;104:1066-9.
83. Svensson A-L, Bucht N, Hallberg M, Nyberg F. Reversal of opiate induced apoptosis by human recombinant growth hormone in murine foetus primary hippocampal neuronal cell cultures. PNAS 2008;105:7304-8.
84. Durrmeyer X, Vutskits L, Anand KJS, Rimensberger PC. Use of analgesic and sedative drugs in the NICU: integrating clinical trials and laboratory data. Pediatr Res 2010;67:117-27.
85. Nassogne M-C, Evrard P, Courtoy PJ. Selective neuronal toxicity of Cocaine in empryonic mouse brain co-cultures. PNAS 1995;92:11029-33.
86. Clowry G, Molnar Z, Rakic P. Renewed focus on the developing human neocortex. J Anat 2010;217:276-88.
87. Yuan Q, Rubic M, Seah J, et al. Do maternal opioids reduce neonatal regional brain volumes? A pilot study. J Perinatol 2014;34:909-13.
88. Nygaard E, Slinning K, Moe V, Due-Tonnessen P, Fjell A, Walhovd KB. Neuroanatomical characteristics of youths with prenatal opioid and poly-drug exposure. Neurotoxicol Teratol 2018;68:13-26.
89. van den Bosch GE, White T, El Marroun H, et al. Prematurity, Opioid Exposure and Neonatal Pain: Do They Affect the Developing Brain? Neonatology 2015;108:8-15.
90. Yazdy MM, Desai RJ, Brogly SB. Prescription opioids in pregnancy and birth outcomes a review of the literature. J Pediatric Genetics 2015;4:56-70.
91. Ornoy A, Michailevskaya V, Lukashov I, Bar-Hamburger R, Harel S. The developmental outcome of children born to heroin-dependent mothers, raised at home or adopted. Child Abuse Negl 1996;20:385-96.
92. Bier JB, Finger AS, Bier BA, Johnson TA, Coyle MG. Growth and developmental outcome of infants with in-utero exposure to methadone vs buprenorphine. J Perinatol 2015;35:656-9.
93. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. Am J Epidemiol 2014;180:673-86.
94. Garrison L, Leeman L, Savich RD, Gutierrez H, Rayburn WF, Bakhireva LN. Fetal Growth Outcomes in a Cohort of Polydrug- and Opioid-Dependent Patients. J Reprod Med 2016;61:311-9.
95. Jones HE, Dengler E, Garrison A, et al. Neonatal outcomes and their relationship to maternal buprenorphine dose during pregnancy. Drug Alcohol Depend 2014;134:414-7.
96. Kelty E, Hulse G. A Retrospective Cohort Study of Birth Outcomes in Neonates Exposed to Naltrexone in Utero: A Comparison with Methadone-, Buprenorphine- and Non-opioid-Exposed Neonates. Drugs 2017;77:1211-9.
97. Visconti KC, Hennessy KC, Towers CV, Howard BC. Chronic opiate use in pregnancy and newborn head circumference. Am J Perinatol 2015;32:27-32.
98. Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. Obstet Gynecol 2015;125:363-8.
99. Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addiction 2016;111:2115-28.
100. Mactier H, Shipton D, Dryden C, Tappin DM. Reduced fetal growth in methadone-maintained pregnancies is not fully explained by smoking or socio-economic deprivation. Addiction 2014;109:482-8.
101. Walhovd KB, Bjornebekk A, Haabrekke K, et al. Child neuroanatomical, neurocognitive, and visual acuity outcomes with maternal opioid and polysubstance detoxification. Pediatr Neurol 2015;52:326-32 e1-3.
102. Sarfi M, Smith L, Waal H, Sundet JM. Risks and realities: dyadic interaction between 6-month-old infants and their mothers in opioid maintenance treatment. Infant Behav Dev 2011;34:578-89.
103. McGlone L, Mactier H. Infants of opioid-dependent mothers: neurodevelopment at six months. Early Hum Dev 2015;91:19-21.

104. Melinder A, Konijnenberg C, Sarfi M. Deviant smooth pursuit in preschool children exposed prenatally to methadone or buprenorphine and tobacco affects integrative visuomotor capabilities. Addiction 2013;108:2175-82.
105. Konijnenberg C, Sarfi M, Melinder A. Mother-child interaction and cognitive development in children prenatally exposed to methadone or buprenorphine. Early Hum Dev 2016;101:91-7.
106. Mactier H. Neonatal and longer term management following substance misuse in pregnancy. Early Hum Dev 2013;89:887-92.
107. Nygaard E, Moe V, Slinning K, Walhovd KB. Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. Pediatr Res 2015;78:330-5.
108. Nygaard E, Slinning K, Moe V, Walhovd KB. Behavior and Attention Problems in Eight-Year-Old Children with Prenatal Opiate and Poly-Substance Exposure: A Longitudinal Study. PLoS One 2016;11:e0158054.
109. Nygaard E, Slinning K, Moe V, Walhovd KB. Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy. Child Neuropsychol 2017;23:159-87.
110. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. BMC Psychiatry 2014;14:104.
111. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Erratum: neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. BMC Psychiatry 2015;15:134.
112. Bernstein V, Jeremy RJ, Hans SL, Marcus J. A longitudinal study of offspring born to methadone-maintained women. II. Dyadic interaction and infant behavior at 4 months. Am J Drug Alcohol Abuse 1984;10:161-93.
113. Marcus J, Hans SL, Jeremy RJ. A longitudinal study of offspring born to methadone-maintained women. III. Effects of multiple risk factors on development at 4, 8, and 12 months. Am J Drug Alcohol Abuse 1984;10:195-207.
114. Jeremy RJ, Hans SL. Behavior of neonates exposed in utero to methadone as assessed on the Brazelton scale. Infant Behav Dev 1985;8:323–36.
115. Johnson HL, Rosen TS. Prenatal methadone exposure: effects on behavior in early infancy. Pediatr Pharmacol (New York) 1982;2:113-20.
116. Lifschltz MH, Wilson GS. Patterns of growth and development in narcotic-exposed children. NIDA Res Monogr 1991;114:323-39.
117. Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age. J Pediatr 1982;101:192-6.
118. Wilson GS, Desmond MM, Wait RB. Follow-up of methadone-treated and untreated narcotic-dependent women and their infants: health, developmental, and social implications. J Pediatr 1981;98:716-22.
119. Hans SL, Marcus J. Motoric and attentional behavior in infants of methadone-maintained women. NIDA Res Monogr 1983;43:287-93.
120. Jones HE, O'Grady KE, Johnson RE, Velez M, Jansson LM. Infant neurobehavior following prenatal exposure to methadone or buprenorphine: results from the neonatal intensive care unit network neurobehavioral scale. Subst Use Misuse 2010;45:2244-57.
121. Heller NA, Logan BA, Morrison DG, Paul JA, Brown MS, Hayes MJ. Neonatal abstinence syndrome: Neurobehavior at 6 weeks of age in infants with or without pharmacological treatment for withdrawal. Dev Psychobiol 2017;59:574-82.
122. Conradt E, Flannery T, Aschner JL, et al. Prenatal Opioid Exposure: Neurodevelopmental Consequences and Future Research Priorities. Pediatrics 2019;144.
123. Hans SL, Jeremy RJ. Postneonatal mental and motor development of infants exposed in utero to opioid drugs. Infant Mental Health J 2001;22:300-15.
124. Levine TA, Woodward LJ. Early inhibitory control and working memory abilities of children prenatally exposed to methadone. Early Hum Dev 2018;116:68-75.
125. Merhar SL, McAllister JM, Wedig-Stevie KE, Klein AC, Meinzen-Derr J, Poindexter BB. Retrospective review of neurodevelopmental outcomes in infants treated for neonatal abstinence syndrome. J Perinatol 2018;38:587-92.
126. Moe V, Slinning K. Prenatal drug exposure and the conceptualization of long-term effects. Scand J Psychol 2002;43:41-7.
127. Moe V, Slinning K. Children prenatally exposed to substances: gender-related differences in outcome from infancy to 3 years of age. Infant Ment Health J 2001;22:334-50.
128. van Baar AL, Soepatmi S, Gunning WB, Akkerhuis GW. Development after prenatal exposure to cocaine, heroin and methadone. Acta Paediatr Suppl 1994;404:40-6.
129. Davis DD, Templer DI. Neurobehavioral functioning in children exposed to narcotics in utero. Addict Behav 1988;13:275-83.
130. Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C. Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. Dev Med Child Neurol 2001;43:668-75.

131. Wilson GS, McCreary R, Kean J, Baxter JC. The development of preschool children of heroin-addicted mothers: a controlled study. Pediatrics 1979;63:135-41.
132. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. Early Hum Dev 2008;84:29-35.
133. de Cubas MM, Field T. Children of methadone-dependent women: developmental outcomes. Am J Orthopsychiatry 1993;63:266-76.
134. Sandtorv LB, Fevang SKE, Nilsen SA, et al. Symptoms Associated With Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorders in School-Aged Children Prenatally Exposed to Substances. Subst Abuse 2018;12:1178221818765773.
135. Yeoh SL, Eastwood J, Wright IM, et al. Cognitive and Motor Outcomes of Children With Prenatal Opioid Exposure: A Systematic Review and Meta-analysis. JAMA Netw Open 2019;2:e197025.
136. Peacock-Chambers E, Leyenaar JK, Foss S, et al. Early Intervention Referral and Enrollment Among Infants with Neonatal Abstinence Syndrome. J Dev Behav Pediatr 2019;40:441-50.
137. Blair C. Educating executive function. Wiley Interdiscip Rev Cogn Sci 2017;8.
138. Guo X, Spencer JW, Suess PE, Hickey JE, Better WE, Herning RI. Cognitive brain potential alterations in boys exposed to opiates: in utero and lifestyle comparisons. Addict Behav 1994;19:429-41.
139. Hickey JE, Suess PE, Newlin DB, Spurgeon L, Porges SW. Vagal tone regulation during sustained attention in boys exposed to opiates in utero. Addict Behav 1995;20:43-59.
140. Konijnenberg C, Melinder A. Neurodevelopmental investigation of the mirror neurone system in children of women receiving opioid maintenance therapy during pregnancy. Addiction 2013;108:154-60.
141. Moe V. Foster-placed and adopted children exposed in utero to opiates and other substances: prediction and outcome at four and a half years. J Dev Behav Pediatr 2002;23:330-9.
142. Walhovd KB, Bjørnebekk A, Haabrekke K, al. e. Child neuroanatomical, neurocognitive, and visual acuity outcomes with maternal opioid and polysubstance detoxification. Pediatr Neurol 2015;52:326-32.
143. Bauman PS, Levine SA. The development of children of drug addicts. Int J Addict 1986;21:849-63.
144. Uebel H, Wright IM, Burns L, et al. Reasons for Rehospitalization in Children Who Had Neonatal Abstinence Syndrome. Pediatrics 2015;136:e811-20.
145. Oei JL, Melhuish E, Uebel H, et al. Neonatal Abstinence Syndrome and High School Performance. Pediatrics 2017;139.
146. Fill MA, Miller AM, Wilkinson RH, et al. Educational Disabilities Among Children Born With Neonatal Abstinence Syndrome. Pediatrics 2018;142:pii: e20180562.
147. Sherman LJ, Ali MM, Mutter R, Larson J. Mental Disorders Among Children Born With Neonatal Abstinence Syndrome. Psychiatr Serv 2019;70:151.
148. Conner KL, Meadows AL, Delcher C, Talbert JC. Neonatal Abstinence Syndrome and Childhood Mental Health Conditions, 2009–2015: Commercial Versus Medicaid Populations. Psychiatric Services 2019;(Advance Publication).
149. Nygaard E, Slinning K, Moe V, Fjell A, Walhovd KB. Mental health in youth prenatally exposed to opioids and poly-drugs and raised in permanent foster/adoptive homes: A prospective longitudinal study. Early Hum Dev 2019;140:104910.
150. Doyle LW, Anderson PJ, Battin M, et al. Long term follow up of high risk children: who, why and how? BMC Pediatr 2014;14:279.

EXHIBIT C

DR. C. V. HOWARD'S DECLARATION IN SUPPORT OF CLASS CERTIFICATION

1)Background

This is a report is prepared for the benefit of the Court.[1] I have been asked to prepare a report addressing the effects of opioids on the developing fetus. I understand my duties as an Expert witness pursuant to Part 35 of the Civil Procedure Rules; a statement of truth is enclosed following my opinion below.

I am a medically qualified toxico-pathologist specialising in the problems associated with the action of toxic substances on health, particularly during the period of development in the womb. My PhD Thesis addressed mechanisms of the selective stabilisation of neurons in developing mammalian brain. I am currently Emeritus Professor of Bioimaging at the University of Ulster and have authored/co-authored over 130 peer reviewed scientific papers, predominantly in the field of quantitative developmental toxicology. I append my Curriculum Vitae.

I am a Fellow of the Royal College of Pathologists, Fellow of the Collegium Ramazzini, Past President of the Royal Microscopical Society, Member of the British Society of Toxico-Pathologists, Past President of the International Society of Doctors for the Environment. I served for 6 years as a toxicologist on the United Kingdom Government DEFRA Advisory Committee on Pesticides which was the statutory body responsible for recommending licensing of agro-chemicals. I have addressed the House of Lords Select Committee on Science and Technology investigating the use of nanotechnology in food. More recently I have given evidence to the House of Commons Environmental Audit Committee on the toxicology of neonicotinoid pesticides to pollinating insects. This resulted in their report 'Pollinators and Pesticides' (HC 668, 2012-13).

Toxico-pathologists are skilled in assessing the effects of toxic substances on health. This includes consideration of routes of entry for toxic substances into the body, assessing the relevance of dose and timing of administration, target organ susceptibility, mechanism of action of toxins, types of pathology induced and dose response, with respect to single substances and mixtures. Such expertise is of relevance in this action because it concerns exposure of the fetus during intra-uterine life to opioids taken by the mother. Opioids have been shown to be able to increase the rate of apoptosis in developing neurons and this has a number of long-term sequelae. This pathological mechanism is within the scope and expertise of toxico-pathologists.

2)The Opioid Receptor (OR)

The opioid receptor system is ubiquitous throughout all vertebrate (animals with backbones) life. Opioid receptors consist of a family of four related proteins which are part of a large superfamily, the rhodopsin-like G-protein coupled receptors. Of the four related proteins, three types of opioid receptor unequivocally are associated with the control of pain in animal models.

[1] This report was developed in collaboration with Dr. Christopher Busby.

These are the □(MOR), □ (DOR) and □ (KOR) opioid receptor proteins. There is a fourth opioid receptor protein which is termed the nociception or orphanin (ORL) whose function is less well defined than the other three. The receptors have natural internally produced (endogenous) opioid peptide ligands which include beta-endorphin, met-and leu-enkephalin and dynorphin. The role of the endogenous opioid receptors on normal physiological activity is extensive; in addition to the obvious role in decreasing painful (nociceptive) sensations they are involved in reproduction, growth, development, respiration, blood pressure regulation, renal function, temperature control, hormonal regulation, seizures, stress, immune response, pregnancy and aging.

Phylogeny:
The OR developed at least 450 million years ago, at the time of the evolutionary emergence of vertebrates with jaws. Early in the evolution of animals there was a single opioid receptor. The first round of genome duplication, which occurred early in cordate evolution, produced the ancestral DOR/MOR and ORL/KOR genes. A further round of genome duplication led to the four opioid receptors found in all living vertebrates (Stevens, 2011). These four ORs are ubiquitous throughout vertebrate phylogeny and intimately involved in the control of reward responses and pain modulation as well as controlling aspects of ontogeny.

3)Opioid Drugs: pharmacology and commonality

Opioids have been used to alleviate pain for thousands of years and remain the most important class of pain-relieving drugs. Opioids exert their effects by mimicking naturally occurring substances in the body, called *endogenous opioid peptides* including *endorphins*. The different functions of this system include
(1) the best-known sensory role—prominent in inhibiting sensory responses to pain
(2) a modulatory role in gastrointestinal, endocrine and autonomic functions, and
(3) and an emotional role, evidenced in powerful rewarding and addictive properties.

Therefore, opioid activity is not restricted to pain relieving effects but in addition exhibit powerful and wide-ranging regulatory roles throughout the organism (Gutstein and Akil, 2006; Stein (2016); Stevens 2011).

In order to understand the effects of the opioids we begin with the production and distribution of the endogenous opioid peptides, since it is these which are mimicked by the opioid drugs which interact with the natural receptors (biological switches). The endogenous opioids are in three distinct families, *the enkephalins, the endorphins and the dynorphins* (Gutstein and Akil, 2006). These substances are small peptides which share a common amino terminal sequence of Tyr-Gly-Gly-Phe-Met (or Leu). This has been termed the *opioid motif* and is followed by various C-terminal extensions yielding peptides ranging from 5 to 31 residues (Gutstein and Akil, 2006).
The precursor protein for Beta Endorphin, *prepro-opiomelanocortin* (POMC) is relatively limited within the Central Nervous System, occurring mainly in the arcuate nucleus and nucleus of the tractus solitarius. These neurons project widely to limbic and brainstem areas and to the spinal cord (Gutstein and Akil, 2006).

The endogenous opioids exert their functions at protein receptors distributed in the brain, and these are the points where the opioid drug molecules, whether natural or synthetic also bind and have pharmacological activity. Opioid receptors consist of a family of four closely related proteins belonging to a large family of receptors called the G-protein coupled receptors. Receptors are large protein molecules which selectively bind pharmacological agents in order to switch on cellular activity that results in a measurable change in some aspect of the cell and the organism. The receptor can be seen as a molecular specific switch. It is believed that specific affinity between the active molecule and the receptor, which occurs only for molecules which can affect the receptor switch positively (termed *agonists*) and produce the effect, defines a class of compounds which have commonality. That is, they have the common molecular nature of causing the process being measured to occur (to a greater or lesser extent). This greater or lesser extent is a function of their *activity* and is measurable. Pharmacologists measure the effect, and plot this against the logarithm of the drug Dose. If the substance is acting at the same receptor, the result is a straight line, (for technical reasons which will not be addressed here). They are termed agonist (for the specific receptor). Compounds which bind to the same receptors but do not cause effects, rather they block the effects of the agonist, are termed antagonists. These also help define a common receptor. More recently, genetic approaches have also characterised families of opioid receptors and described their evolution in both mammalian and invertebrate evolution. Therefore, it is possible to say that the opioids and synthetic opioids, whatever their molecular structure, exert their influence at the same receptor(s) and may thus be considered as a common group (Creeley et al, 2013; Gutstein and Akil, 2006).

There are now considered to be three main types of receptor, termed classical types, the μ, κ and δ. All three have analgesic properties, the μ type causes euphoria, decreases respiratory function and gastrointestinal tract transit (constipation), increases feeding, increases sedation, increases release of growth hormone and prolactin, inhibits neurotransmitter release (acetylcholine and dopamine) and has various other peripheral effects. These examples show the profoundly powerful effects throughout the organism which are modulated by the opioids. It also shows how exposure to, and withdrawal from these species exhibits such wide-ranging effects. All three opioid receptors can modulate pre- and post- synaptic Ca++ channels, supress Ca++ influx and thereby attenuate the excitability of neurons and the release of pro-nociceptive neuropeptides (Gutstein and Akil, 2006). This behaviour is revisited below.

Identity and molecular structure of the opioids (https://webbook.nist.gov/cgi/cbook/).

The medicinally developed opioids are in two groups, those derived from natural products by chemical treatment or separation and those developed by chemical synthesis in order to have affinity and access to the various opioid receptors discussed. The search by pharmaceutical companies and others for substances which produced the analgesic and other valuable effects without side effects or the induction of dependence has been largely unsuccessful. Investment in research into substances which would act as treatments for addiction to morphine and the more powerful narcotic opioids resulted in the discovery and use of methadone and buprenorphine. However, these themselves also result in addiction and withdrawal effects. They are the agents of choice in some schemes of treatment for NAS. The molecular structures of all these compounds are designed to have affinity for the opioid receptors and therefore may

be considered to be one group for the purposes of arguing their membership of the "NAS producing group" of chemical substances. Most of them are semi-synthetic compounds made by chemical treatment of morphine itself or morphine alkaloids like Thebaine (Gutstein and Akil, 2006; O'Brien, 2006; Oates, 2006).

The principal opioids of concern in the current discussion are given in Table 1.

Table 1. Principal opioids associated with NAS (*examples of trade preparations*) [https://webbook.nist.gov/cgi/cbook/].

Opioid	**Nature**	**Note**
Morphine	Main alkaloid constituent of opium; historic medicinal compound. *Avinza, Morphabond, Roxanol-T, Kadian, Mscontin*	Natural substance, main member of the opium poppy alkaloids which also include Thebaine Papaverine.
Hydrocodone	derived from morphine alkaloids. Semi synthetic. *Zohydro ER, Hysingla, Anexsia, Co-gesic, Ibudone, Norco*	Semisynthetic hydrogenated codeine derivative and opioid agonist with analgesic and antitussive effects. Hydrocodone primarily binds to and activates the mu-opioid receptor in the central nervous system (CNS).
Hydromorphone	Also called Dilaudid. Hydromorphone is the hydrogenated ketone of morphine, semi synthetic. *Dilaudid, Palladone,*	Hydromorphone selectively binds the mu-opioid receptor which is linked through G-proteins. Binding stimulates the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) on the G-protein complex and interacts with and inhibits adenylate cyclase located at the inner surface of the plasma membrane. This leads to a reduction in intracellular cyclic 3',5'-adenosine monophosphate (cAMP). Further, voltage-gated potassium channels are activated, thereby causing hyperpolarization and reducing neuronal excitability. In addition, the opening of voltage-gated calcium channels is inhibited, thereby leading to an inhibition of calcium entry and a reduction in the release of various neurotransmitters, including GABA, vasopressin, somatostatin, insulin and glucagons.
Meperidine	Synthetic *Demerol*	Meperidine is a synthetic piperidine ester with opioid analgesic activity. Meperidine mimics the actions of endogenous neuropeptides via opioid receptors, thereby producing the characteristic morphine-like effects on the mu-opioid receptor, including analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia and physical dependence.
Fentanyl	Synthetic *Abstral, Actiq, Fentora, Onsolis, Sublimaze, Duralgesic*	Powerful synthetic opioid 100 times more powerful than morphine in pain relief
Codeine	Derived from morphine by methylation of the phenolic -OH.	Naturally occurring phenanthrene alkaloid and opioid agonist with analgesic, antidiarrheal and antitussive activities. Codeine mimics the actions of endogenous

		opioids by binding to the opioid receptors at many sites within the central nervous system (CNS). Stimulation of mu-subtype opioid receptors results in a decrease in the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline; in addition, the codeine metabolite morphine induces opening of G-protein-coupled inwardly rectifying potassium (GIRK) channels and blocks the opening of N-type voltage-gated calcium channels, resulting in hyperpolarization and reduced neuronal excitability. Stimulation of gut mu-subtype opioid receptors results in a reduction in intestinal motility and delayed intestinal transit times. Antitussive activity is mediated through codeine's action on the cough center in the medulla
Buprenorphine	Synthetic analogue of Thebaine from poppy alkaloids *Butrans*	Buprenorphine is a morphinane alkaloid that is 7,8-dihydromorphine 6-O-methyl ether in which positions 6 and 14 are joined by a -CH2CH2- bridge, one of the hydrogens of the N-methyl group is substituted by cyclopropyl, and a hydrogen at position 7 is substituted by a 2-hydroxy-3,3-dimethylbutan-2-yl group. It has a role as an opioid analgesic, a mu-opioid receptor agonist, a kappa-opioid receptor agonist and a delta-opioid receptor antagonist.
Methadone	Synthetic *Dolophine, Methadose*	Methadone is a synthetic opioid with analgesic activity. Methadone mimics the actions of endogenous peptides at CNS opioid receptors, primarily on the mu-receptor and has actions similar to those of morphine and morphine-like agents. The characteristic morphine-like effects include analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia and physical dependence. However, the detoxification symptoms between morphine-like agents and methadone differ in that the onset of methadone's withdrawal symptoms is slower, the course is more prolonged and the symptoms are less severe.
Oxycodone	Semi synthetic. Derived from opium alkaloid Thebaine. *Oxaydo, Xtampza ER, Oxycontin, Percodan, Percoset,*	Oxycodone is a semi-synthetic, morphine-like opioid alkaloid with analgesic activity. Oxycodone exerts its analgesic activity by binding to the mu-receptors in the central nervous system (CNS), thereby mimicking the effects of endogenous opioids.
Oxymorphone	Semi synthetic. Now taken off market in USA (2017) *Opana, OpanaER*	A semisynthetic opioid with a potent analgesic property. Oxymorphone hydrochloride binds to and activates opiate receptors, specifically mu-receptors, in the central nervous system (CNS).
Heroin	Semi synthetic. Illegal in USA.	Heroin is a morphinane alkaloid that is morphine bearing two acetyl substituents on the O-3 and O-6 positions. As with other opioids, heroin is used as both an analgesic and a recreational drug.

Summary of pharmacology

The opioid compounds all act at the same biological receptors and mimic natural peptides which have powerful and wide-ranging activity in living systems. Thus, they can be considered a class of chemical drugs both in terms of their pharmacological dosage activity relationships and also their overall chemical structure. They produce common effects, bind to common receptors, the opioid receptors and also have similar chemical structures. They all produce addiction and dependence and cause withdrawal symptoms on removal. Their activity as modulators of neurological signalling make them especially hazardous in adults due to rebound effects but also they are now known to have significant effects on foetal development since they alter the cellular signalling environment. This issue will be considered below.

4)Dependence and withdrawal in opioids: pharmacology (O'Brien, 2006)

All perturbations of homeostatic systems that last a significant length of time result in two responses. The first is acquired tolerance, which results in a situation where larger doses of the stressor (in this case the opioid drug) are required to effect the same physiological response. The second results from the homeostatic pressure developed by the organism to retain the system's biological status prior to the disturbances created by the perturbation, in this case the chronic use of an opioid drug and the changes brought about in the various systems affected by the receptors. This physical dependence is often termed "Rebound" and is a common feature of withdrawal of all drugs which have Central Nervous System (CNS) effects. Thus, CNS hyperarousal results from re-adaptation to the absence of the drug of dependence (O'Brien, 2006). Since the effects produced by the opioids are so widespread (due to the systems that are perturbed through the 3 natural opiate receptors (at least these: more have been described) the withdrawal of the opioid alteration pressure leads to profound and painful mental and physical effects across a wide spectrum of conditions. Examples of the effects seen in adults are given in Table 2. In Table 3 are listed withdrawal effects seen in babies manifesting NAS. Naturally the same rebound effects are manifest in the babies as exist in the adults.

Table 2 Withdrawal effects in adults seen in opioid removal after chronic use **(O'Brien, 2006)**

Regular withdrawal	**Protracted withdrawal (persist up to 6 months after removal of drug)**
Craving for opioids	Anxiety
Restlessness, irritability	Insomnia
Increased sensitivity to pain	Drug craving

Nausea	Pupillary dilation
Cramps	Sweating
Muscle aches	Piloerection
Dysphoric mood	Tachycardia
Insomnia	Vomiting
Anxiety	Diarrhia
	Yawning
	Fever
	Cyclic changes in weight
	Pupil size

Table 3 Observed NAS withdrawal effects (Wolff K, Perez Montenajo R, 2014)

Effect	**Number of studies reporting 1972-2007**
Neurological Excitability	
High pitched crying	8
Irritability	8
Increased wakefulness/sleep disturbance	8
Hyperactive deep tendon reflexes	9
Hypertonia	6
Exaggerated Moro Reflex	3
Tremors	9
Seizures	9
Myoclonic jerks/ opisthotonic posturing	5
Hyperacusis	1
Intraventricular haemorrhage	1
EEG abnormalities	1
Gastrointestinal dysfunction	
Poor feeding	8
Uncoordinated and constant sucking	7
Vomiting	10
Diarrhoea	10
Dehydration	4
Regurgitation	1
Poor weight gain/ weight loss	6
Hyperphagic (2^{nd} week)	0
Excessive salivation	1
Central nervous system	
Increased sweating	8
Yawning	9
Nasal stuffiness	5
Sneezing	9
Tachypnea	6
Mottled skin	5
Fever	7
Temperature instability	3
Other	
Increased REM sleep	2

Skin excoriating/ scratching	5
Tachycardia/ hypertension	1

These effects are common to withdrawal in the case of all the opioids since these substances act on the same receptors. Of course, there are differences in activity between the various opioid drugs, some having very powerful effects at very low doses relative to morphine, the parent substance, and there is also a variation in the length of time the compound has its effect owing to variations in length of binding to receptors and other factors. The drug Methadone has a much longer period of action so it was chosen (or indeed developed) to act as a drug of choice for dealing with withdrawal from the more immediate effects of morphine and in particular the street drug Heroin. Buprenorphine also has a similar long lasting effect and is used as an alternative to Methadone for reducing the withdrawal effects listed in Tables 2 and 3. However, since both these drugs affect the same receptors that cause the withdrawal effects, it is arguable that their use may produce the same conditions that they are intended to treat. A list of analgesic activity for the various opioids is given in Table 4.

Table 4 Equianalgesic doses for some opioids.

Compound	**Route**	**Dose mg**
Codeine	PO	200
Hydrocodone	PO	20-30
Hydromorphone	PO	7.5
Hydromorphone	IV	1.5
Morphine	PO	30
Morphine	IV	10
Oxycodone	PO	20
Oxycodone	IV	10
Oxymorphone	PO	10
Oxymorphone	IV	1
Fentanyl	Nasal spray/ lozenge	0.1-0.2

5)Apoptosis

It is important to introduce an aspect of basic biology which is of fundamental significance in fetal development. There are two ways in which cells in multicellular organisms can die. One is called ‘necrosis’ – for example if one of the coronary arteries blocks and deprives the heart muscle of oxygen, it will die by necrosis – which is a pathological process. The other mechanism is called ‘apoptosis’, otherwise known as ‘programmed cell death’. This is part of normal biology, particularly during development. For example, almost all individuals had a tail at one stage of fetal life but in almost everybody it melts away by the process of programmed cell death. The hands were solid discs of tissue in their early development but the fissures between the digits appear because of apoptosis remodelling the original disc. There are three basic functions that apoptosis serves:

1) Phylogenetic apoptosis – deletion of vestigial structures
2) Histogenetic apoptosis – controlling cell numbers in the body

3) Morphogenetic apoptosis – remodelling structures

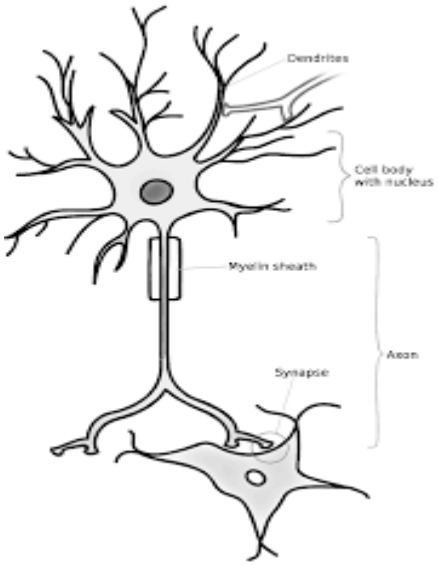
Histogenetic apoptosis is the predominant mode found in the adult. Phylogenetic and morphogenetic apoptosis predominate in the fetus and are indispensable for normal development. Sub optimal brain development and gross malformations (birth defects) have been associated with perturbations of apoptosis.

The Central Nervous System (CNS)

It is important that animal experimental data, as well as human data, is considered when addressing the impact of opioids on developing human brain. Opioid receptors are present in a number of different brain regions and there are several possible mechanisms that opioid exposure could perturb brain development (Yanai et al., 2003). Alterations in the migration and survival of neurons in rat embryos has been demonstrated with exposure to opiates (Harlan, R. E. & Song, D. D., 1994). In vitro studies on human fetal neurons and microglia responses to morphine have been shown to have increased levels of apoptosis [Hu et al., 2002). Reduction in anatomical volumes and cortical thickness when compared to controls in children with heroin and polysubstance exposure

The central nervous system is particularly vulnerable to toxic insult for a number of reasons. The nerve cells that are a component of the adult brain have to last a life time. The adult neuron has a cell body from which a single axon (final common pathway) arises and this conducts a pulse modulated signal on to the next nerve cell in the chain. Whether or not a neuron depolarises to produce the next pulse in the signal chain going down the axon depends on an averaging of all synaptic inputs, excitatory and inhibitory, over the whole receptive surface of the nerve cell, which includes the cell body and the dendritic tree.

Many other organs in the body, for example the liver, can repair by cell proliferation. This does not apply to the nerve cells in the adult CNS, by far the majority of which cannot reproduce themselves. This statement does not hold true for the fetal brain nerve cells, as will be outlined below. The CNS has a very high metabolic rate and neurons have to maintain their microstructures over long distances. For example the axon, which carries outgoing signals from the neuron can be over 1 meter long. To maintain such structures in a healthy state there is a mechanism called ‘axonal transport’ which will deliver a number of substances and structures – in both directions to and from the neuron cell body. Transmitter substances help to deliver information across synapses to the next neurons in the neuronal chain by acting in either an excitatory or an inhibitory manner. The influence of a particular synaptic input onto a neuron will depend on its position on the target neuron and on the firing rate of the axon. ‘Neurotrophins’ are also secreted across the synapse and are essential to maintain the target neurons in good health. Mitochondria are the ‘powerhouses’ in which glucose is metabolised and maintain the high metabolic rate essential for neuronal health, even in the most distant parts of the nerve cell. ‘Neuromodulators’ are a class of biomolecules, to which the endogenous opioids belong, modify the action of transmitter substances at synapses.



6)The relevance of perturbing apoptosis in fetal brain

There are of the order 1015 connections between nerve cells in the adult human central nervous system (CNS). However, humans only have ~ 20,000 genes, which in addition also have to control many other aspects of development. This inevitably means that the development of the brain cannot be determined by the genome alone – there is a massive numerical mismatch. Therefore, nature has evolved a method of arriving at an intact functioning CNS which depends upon a highly probabilistic (chance) based mechanism, which is relatively loosely specified by the genes. The genes control the overall global form of the brain while, at the local level, whether developing cells live or die is decided predominantly by chance.

The importance of synapse formation in the development of brain circuitry was first posited by Changeaux and Danchin (1976) in their theory of 'selective stabilisation'. A more contemporary review has been written by Tau & Peterson (2010). Selective stabilisation involves the loss of a proportion the neurons in a developing brain region, based upon their functional status during critical developmental windows.

In the developing nervous systems of animals (including humans) there is an overproduction of neuroblasts (immature potential neurons) – often more than twice as many as will be finally required in the adult. These start to push out neurites (fibre-like feelers) that make contact with other developing nerve cells in that brain region. Some of the contacts they make at random will be excitatory and others will be inhibitory. At certain developmental times, cell signalling instructions will be broadcast within regions of the CNS and those nerve cells with the correct physiological properties (for example the firing rate of the nerve cell) will carry on with their normal development and the other developing nerve cells which are either under-responsive or over-responsive will undergo apoptosis and melt away. This process is known as 'selective stabilisation'. From this description it can be appreciated that this is largely based on chance connections between too many potential neurons and it leads to a stable functioning circuitry within the CNS with minimal deterministic instructions at the local level from the genes. The mechanism(s) controlling apoptosis in the developing fetal

brain are incompletely understood. However, many cell signalling molecules –including transmitter substances, neuromodulators and hormones are known to be involved. An important harbinger of impending apoptosis in a cell is the appearance of Fas protein being expressed on the cell surface. When this binds with Fas protein ligand (FasL) apoptosis is initiated.

From all of the above it is possible to appreciate how a drug that stimulates nerve cells could act as an 'excitotoxin' in the fetal brain while a neuronal depressant would work the other way. Both of these scenarios result in increases in the proportion of nerve cells undergoing cell death though apoptosis during windows of vulnerability as fetal development progresses. The final outcome in the adult, if this happens, will be sub-optimal development. Reed et al (2010) provide a morphological example. Opioids appear to increase the rate of apoptosis in fetal brain. This is a potential mechanism for neurological damage in the fetus.

Important points to note are:

1) Adverse changes incurred through increased apoptosis are irreversible
2) They generally take place at toxicant concentrations orders of magnitude lower than required to produce damage in an adult.
3) The timing of the toxic insult in the fetal developmental timetable is critical, as it passed through sequential windows of vulnerability

The effects of prenatal exposure to opioids has been reviewed by Anand and Cambell-Yeo (2015). It leads to changes in the temporal sequencing and quality of myelination by disrupting oligodendrocyte development (Svensson et al, 2008). It also decreases the dendritic growth (Nassogne et al, 1885)) and branching pattern complexity (Broussard et al, 2011) of pyramidal neurons in the cortex and suppresses cell proliferation and neuronal migration to the cortical plate. These effects may reduce regional brain volumes in the basal ganglia (McCarthy, 2015) and other brain areas (Yazdy et al, 2015), with long-term changes in subsequent behaviour (Patrick et al, 2015; Bignami et al, 1996; Kavlock et al, 1995), autonomic regulation (Patrick et al, 2015), visual-motor (Moe, 2002), strabismus (Gill et al, 2003), or swallowing (Gewolb et al, 2004) dysfunctions and lower developmental potential (McGlone & Mactier, 2015; Robinson, 2002; Tempel & Espinoza, 1992). Current data cannot clearly differentiate between the long-term neonatal outcomes resulting from the prenatal use of prescription opioids, illicit drugs or opioid maintenance therapy. Buprenorphine and methadone form the mainstay of opioid maintenance therapy during pregnancy. Buprenorphine is considered an attractive alternative, partly due to more favourable neonatal brain growth patterns (Welle-Strand et al, 2009); however, its long-term use cannot be considered benign and has been associated with poor child outcomes to three years of age (Kivisto et al, 2015).

7)The relevance of perturbing apoptosis to gross anatomical malformations

Beginning in the late 1990's the understanding of the mechanism of foetal development began to undergo a significant change through research which identified and defined the concept of

Apoptosis, or programmed cell death (Kerr et al, 1972; Jacobsen et al, 1997; Bartlett, 2018; Mazarakis et al, 1997; Olney et al, 2000). Jacobsen identified the importance of apoptosis in foetal development in 1997. The process itself was described by Kerr et al in 1972 and the Nobel prize for the discoveries was awarded in 2002. It appeared that the foetus developed though the various foetal stages (which have been likened to evolutionary development of the human) by producing an enormous number of pluripotential cells, hugely more than are necessary, which are then selected though signalling from a set of chosen or pre-programmed cells to commit suicide. Research using animal and cell culture models illustrated a developmental plasticity which was controlled by signalling between cellular communities which became ultimately part of organ systems and neurological and other systems through switching off what were deemed to be superfluous or incorrect cells.

The system was controlled by signalling between cells. And since signalling between cells is also the domain of cell receptors and endogenous molecular ligands (for example the neurotransmitter molecules, the small peptide hormones like the endogenous opioids) it was clear that alteration of the developmental landscape through the addition of foreign agents with the ability to alter the sensitivity of the cell communication systems must also carry a serious risk of causing developmental effects, both hidden and morphologically clear in the baby at or after birth.

This problem was quickly addressed through research in the late 1990s and early 2000s since it was clear at that stage that theoretically, the possible causes of major congenital malformations but also hidden neurological, neuropsychiatric and psychosocial effects in children might follow from agents which were not themselves mutagens but which acted by altering the signalling environment during foetal development. It turned out very quickly that almost any agent which affected the homeostatic equilibrium of neurological (and indeed all) development when introduced to the foetus because of the mothers' exposure could cause such effects (Olney et al, 2000). The "teratogenic" effects of alcohol intake and smoking had already been described, though not explained mechanistically.

The opioids operate at the endogenous opioid receptors in the brain, the nervous system and other parts of the organism, as has been pointed out above. The opioid receptors are G-protein coupled receptors. Neural stem cells (cells that develop into the brain and nervous system) are self-renewing and pluripotent cells which give rise to the cells that ultimately make up the brain and nervous system: neurons, astrocytes, oligodendrocytes. In the developing cerebral cortex, neural stem cells differentiate into more committed progenitor cells and migrate into the regions where they lay down the basic structures that finally define the individual. Time lapse images show that cells migrate to the positions where they finally remain in various ways. G-Protein coupled receptors constitute the largest family of transmembrane receptors and are responsible for converting a diverse array of extracellular stimuli into intracellular signalling events. They are involved in a variety of physiological processes such as proliferation, differentiation and migration.

It would therefore have been predictable that the perturbation of the developmental environment by the addition of powerful agents to the extracellular matrix, compounds which have affinity and activity at the G-protein opioid receptors would result in developmental

alterations. And laboratory studies demonstrated such effects (Mizuno et al, 2005). The essential nature of apoptosis in the normal development of palatal fusion is provided by Cuervo (2002). Mid-line fusion defects result from perturbed apoptosis. The importance of apoptosis in the normal development of the heart has been reviewed by van den Hoffa et al (2000). They also reviewed the importance of apoptosis in the effects of teratogens in the production of cardiac malformations.

As pointed out, the role of apoptosis in neural development and disease was described by 1997. This is of interest for the current case since the pharmaceutical companies which were marketing the opioids to pregnant mothers should have realised the potential for serious developmental problems in the foetus which were clear from the reviews which appeared by then (Mazarakis et al, 1997).

However, by the early 1990s it had been already suggested, through a significant body of research, that Cocaine (another G-protein agonist) exposure in utero caused serious alterations in the development of the central nervous system, with major downstream effects implied for the baby and child, including microcephaly and post-natal signs and conditions which were largely the same as those reported for the NAS babies (Nassogne et al, 1995). The question of occult neurophysiological and psychosocial sequelae was clearly implicit.

Evidence that opioids behaved as they were predicted to and caused major birth defects appeared in the results of the National Birth Defect Prevention Study published in 2010 (Broussard et al, 2011; McCarthy, 2015). The study looked at 17,449 cases and 6701 controls. Statistically Significant effects were found for associations between early pregnancy maternal opioid analgesic treatment and certain birth defects, notably heart defects, anencephaly, cleft palate and spina bifida. A list of the most notable birth defects and their Odds Ratios (the ratio between cases and controls) is given in Table 5.

Table 5 Association between maternal opioid analgesic treatment and specific major birth defects in National Birth Defects Prevention Study of 17449 cases and 6701 controls. Significance is starred * in the usual way (Broussard et al, 2011). Odds ratios were adjusted for maternal age, race/ethnicity, education, pre-pregnancy obesity, smoking.

Birth defect	Total no	Odds Ratio (95%CI)
Anencephaly	9	1.7 (0.84-3.4)
Spina bifida**	26	2.0 (1.3-3.2)
Any included heart defect***	211	1.4 (1.1-1.7)
Atrioventricular septal defect*	9	2.4 (1.2-4.8)
Conotruncal defects*	41	1.5 (1.0-2.1)
Tetrology of Fallot*	21	1.7 (1.1-2.8)
Ventricular septal defect*	6	2.7 (1.1-6.3)
L ventricular outflow obstruction*	36	1.5 (1.0-2.2)
Hypoplastic Left heart syndrome**	17	2.4 (1.4-4.1)
R ventricular outflow obstruction*	40	1.6 (1.1-2.3)
Pulmonary valve stenosis**	34	1.7 (1.2-2.6)
Cleft palate	25	1.3 (0.84-2.4)
Hydrocephaly*	11	2.0 (1.0-3.7)

Esophageal atresia	12	1.4 (0.76-2.5)
Gastroschisis*	26	1.8 (1.1-2.9)
Anorectal atresia/ stenosis	18	1.5 (0.9-2.4)
Diaphragmatic hernia	12	1.2 (0.66-2.2)

The study noted that the main results were associated with exposures to Codeine but positive results were also found for Hydrocodone, Oxycodone and Meperidine. Since the mechanism for these effects was by then well described and implicit in the research that had emerged from 1990 onward about neurodevelopment mechanisms, it should have been apparent to those marketing and selling the opioid drugs that warnings should have been given to those prescribing them and to those women taking them. These warnings should have been included in the labelling of the preparations.

8)Communications between the FDA and pharmaceutical companies on opioid teratogenesis.

In connection with this, I have read the following documents:

-ABDCMDL00002835_-Mallinckrodt Fentanyl Transdermal Patch Labelling
-JAN-0003-0002176 - Proposed Label Changes for Pregnancy- Tapentadol
-Acquired_Actavis_00184044_-Suboxone/Bupenorphine Labelling
-ACTAVIS0229401_-Actavis Fentanyl Transdermal Patch labelling
-CAH_MDL_PRIORPROD_DEA07_00870865_-Palladone Hydromorphone Insert Labelling
-END00212911_-Opana Labelling
INSYS-MDL-000325903_-Morphine Sulphate Provider Insert
PAR_OPIOID_MDL_0000331039-Hydrocodone Ibuprofen Insert

Observations

The responses of the different companies are remarkably consistent, there is very little variation in what has been presented. There are warnings about the consumption of opioids in women who are pregnant or are of child bearing age. The general advice is that the risks to the fetus have to be weighed up against other possible clinical benefits. Nowhere is there the suggestion that any opioid should not be prescribed during pregnancy.

The risk of teratogenesis in the animal studies cited by the manufacturers is largely explained through the mechanism of maternal toxicity rather than a direct teratogenic effect. I have not seen the studies that were relied upon but understand that these studies have not been released under discovery and are not available in the public domain. It is therefore difficult to make an objective assessment of the methodologies applied and the conclusions drawn.

However, it has been argued that if there is no teratognesis at the equivalent of 2x the human dose (on a body surface area basis) or ~ 5 x (on a body weight basis) then it is implied that there is nothing of concern and that opioid medicines should be safe for the medical profession to prescribe to pregnant women. Only gross anatomical malformations seem to

have been considered as toxicological endpoints. Functional deficits, particularly in the nervous system, generally occur at lower doses that those required to produce gross malformations and this has not been alluded to in communications between the FDA and the pharmaceutical companies.

There are a number of criticisms of this approach. Allometric scaling between different species is routine in toxicology. Some of the reasons for needing to do this are:

- Larger animals have lower metabolic rates
- Physiological process of larger animals is slower
- Larger animals required smaller drug dose on weight basis
- Allometry accounts for the difference in physiological time among species
- Allometric scaling is not valid to convert adult doses to fetal or infant doses.

Commonly accepted allometric conversion factors between species are:

Human dose (mg/kg) to mouse dose (mg/kg) - multiply by 12.3

Human dose (mg/kg) to rat dose (mg/kg) - multiply by 7.4

Human dose (mg/kg) to guinea pig dose (mg/kg) - multiply by 4.6

Human dose (mg/kg) to rabbit dose (mg/kg) - multiply by 3.1

Human dose (mg/kg) to dog dose (mg/kg) - multiply by 1.8

For rat and mouse, these allometric scaling ratios of 7.4 and 12.3 respectively, seem to have been ignored in communications to the FDA.

Examples of physiological differences between children and adults that may be significant in terms of toxicological response and which may not scale proportionally or continuously with body weight include the following:

• Respiration rate,

• Glomerular filtration rate,

• Active gastrointestinal absorption of nutrients,

• Composition and activity of intestinal flora

• Percentages of body fat and body water,

• Levels of CYP 450 isoforms and other phase I enzymes,

• Glucuronic acid conjugating ability, Phase 2 enzymes do not reach an efficient level in the infant until about 6 months post-natally.

• Biliary excretion ability, and

• Rates and patterns of growth in particular organs (bones, brain, immune system, etc.) which represent windows of vulnerability for damage during the developmental process.

Regulatory Toxicology

As well as the standard toxicology outlined above, there is an additional consideration that needs to be addressed. The rules of acceptance of a medication under informed consent, though they do apply to the mother, they do not apply to the fetus. In this scenario the fetus is receiving an outside agent, an opioid, which is certainly not being administered for the therapeutic benefit of the fetus. It could therefore be regarded, in this respect, as an external toxic agent.

When considering toxic agents in other life settings, for example pesticide residues on food, regulatory toxicologists try to estimate a 'No Effect Level' (NOEL) from the experimental evidence for a particular toxic agent. This NOEL is then subject to 'Uncertainty Factors' (UFs) which are typically x10 for species difference (when the data comes from a laboratory animal) and a further x10 because of inter-individual variability between humans. Therefore, the NOEL is divided by 10 x 10 = 100 to arrive at Tolerable Daily Intake (TDI). However, in the case of infants and fetuses there is sometimes an additional UF of x 10 applied to account for the additional vulnerability to harm associated with the developmental period. Under this condition the NOEL would have to be divided by 10 x 10 x 10 = 1,000 to arrive at a TDI. An example of this is provided under the US EPA Food Quality Protection Act (FQPA) which applies a UF of 1,000 in the case of infant exposures to toxic xenobiotics in food.

If the experimental data indicate that there is no safe dose then a NOEL cannot be determined and a regulatory TDI cannot be set. Examples of this is are provided by radiation exposure and genotoxic substances.

This brief overview of the regulatory toxicology approach highlights the inadequacy of the safety data put forward by the pharmaceutical industry to the FDA. In my opinion, the risk to the fetus has been understated.

9)Epigenetic effects of opioids

A Mini-Review by Gilardi et al (2018) 'Will Widespread Synthetic Opioid Consumption Induce Epigenetic Consequences in Future Generations?' discusses the animal experimental and human data currently available. Epigenetic changes can alter and regulate the way certain genes express themselves in the absence of mutations. This is achieved by remodelling the structure of the chromatin from 'open' (transcriptionally active) to 'closed' (transcriptionally inactive). A number of molecular mechanisms exist, including DNA methylation and post-translational modification of histones.

The review, while acknowledging the lack of transgenerational studies, "converging evidence suggests that opioids can induce long-lasting transgenerational changes in subsequent generations, particularly concerning drug sensitivity and tolerance, with possible implications for drug abuse vulnerability". A major part of this 'converging evidence' is the animal experimental data that Is available.

It is my opinion that epigenetic transgenerational effects should be considered in any future monitoring program of NAS sufferers

10)Causation – Sir Bradford Hill's methodology

In Bradford Hill's still widely used seminal paper of 1965i, which focuses on how we can move from an observed association to a robust causal inference, he identified nine "features" (often misnamed as "criteria") of the available, and often "ragged", evidence (Vandenbroucke J, Broadbent A & Pearce N, 2015) which, if present, could help justify a robust causal inference. Bradford Hill was careful to point out that even if these features of the evidence (Table 6) were absent, then that did not justify concluding that the agent being evaluated was not causing harm. In other words, the features of the evidence were asymmetrical, a word he did not use despite making the conceptual point very explicit when discussing several of the features of the evidence (Gee, 2008).

Bradford Hill would have approached the evidence with: "the decisive question… whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A?". In this case event B is the diagnosis of NAS and the subsequent negative sequelae. Event A is the exposure of the pregnant mother to opioids.

From Table 6 I conclude that the overall weight of evidence supports a causal link between maternal opioid exposure during pregnancy and the appearance of NAS in the neonate. In my opinion, the causal relationship is strong and is beyond 'more likely than not' i.e. at or around the "balance of probabilities", or the "fair" strength of evidence, which Bradford Hill considered a sufficiency of evidence to justify preventative measures.

Table 6 - The Bradford Hill Approach Applied to NAS

Strength of association: case studies & clinical data indicate clear health impacts in significant proportions of exposed groups
Consistency: The clinical data is consistent with the known action of opioids and is similar across international boundaries.
Specificity: NAS is a syndrome with common neurological symptoms linked to maternal opioid exposure during pregnancy.

Temporality: Opioids have been present throughout recorded human history and therefore it is not possible to establish the position prior to regular human exposure. There is a temporal link in that there has to be maternal opioid exposure prior to the appearance of NAS in the resulting neonate.

Biological gradient: higher maternal opioid exposure often causes greater health effects; but lower dose effects also apparent, suggesting non -linearity

Plausibility: the known effects of opioids through the opioid receptor, which is universally present, support a causal link.

Coherence: animal/human data support a causal link

Experiment: animal experimental data supports a causal relationship between maternal opiate exposure and teratogenic effects (fetal malformations, functional neurological damage) through the principal mechanism of increased apoptosis.

Analogy: Maternal exposure to other teratogenic agents during pregnancy leading to both functional and anatomical teratogenesis; eg lead, mercury, di-ethyl stilbestrol, thalidomide.

11)Summary and opinion

Opioids all act in common through the opioid receptor system, which is universally present in vertebrate life forms and is well conserved throughout their evolutionary history. Therefore, this class of drugs has a common mode of action.

Opioid pharmaceutical agents affect the rate of apoptosis in development. The rate of apoptosis (programmed cell death) is critical for the normal development of the fetus and perturbing that rate will lead to teratogenesis, both morphological and functional. Therefore, there is a recognised pathological mechanism in common across this class of pharmaceutical agents.

There are no questions concerning foetal opioid dose to address. The Plaintiffs in this Class Action all had significant exposure to pre-natal opioid pharmaceuticals via their mothers. This was at a level which subsequently led to the postpartum diagnosis of NAS. This diagnosis is casually linked with a higher risk of suffering a congenital malformation. It also causally linked with a higher risk of neurological damage which could be expressed through various latent negative health impacts. These are the reasonably certain consequences of their

exposures, which are the result of subcellular or other physiological changes and can also be manifested in physical or mental injury or disease.

Prescribing opioids to women during pregnancy will lead to fetal damage. This is because of the known toxicity of opioids to the fetus which leads to increased risk of latent disease in the child post-natally. This should be made clear to women of child bearing age who are on opioid maintenance therapy and who are at risk of becoming pregnant. In my opinion, regimes for maternal opioid withdrawal should be considered as a primary part of any risk benefit considerations. The manufacturer's submissions to the FDA do not indicate any support for this approach which, in my opinion, did not reflect known risks of neurologic, developmental or teratogenic effects.

The establishment of Scientific Panels to participate in a medical monitoring program would, in my opinion, be beneficial for the following reasons. Monitoring for the post-natal consequences NAS is reasonable and necessary, according to contemporary scientific principles. The monitoring program should include periodic diagnostic medical examinations as there is clinical value in early detection and diagnosis. Therefore, this is different from a typical post-natal monitoring regime in the absence of exposure. The collection of prospective epidemiological data from a large cohort of NAS sufferers will lead to very robust studies that will deliver a medical benefit to a wider group of NAS sufferers than just those who have received prescription opioids during pregnancy. There will be beneficial read-across data that is relevant to other classes of opioid exposed fetuses. Such Scientific Panels should be composed of experts from the multiple medical and scientific disciplines that are required to fully understand this complex condition, including (but not necessarily restricted to): paediatricians, epidemiologists, physicians specialising in opioid addiction, psychiatrists, behavioural psychologists, toxico-pathologists, neurobiologists.

In my opinion, on the balance of scientific and medical probabilities, these negative outcomes are attributable to the treatment of the mothers with opioids. This includes treatment of mothers-to-be prior to pregnancy, when addictions can be established, and then during pregnancy at a dose adequate to induce NAS in their infant, via the common mode of action of this class of medicines and through the common pathological mechanism identified.

12)Statement of Truth

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Dr. C.V. Howard 02/12/2019

References

Anand KJS & Campbell-Yeo M. Consequences of prenatal opioid use for newborns. Acta Pædiatrica. 2015 104: 1066–1069

Bains R.K., Sibbons P.D., Murray R.D., Howard C.V. van Velzen D. (1996).'Stereological estimation of the absolute number of glomeruli in the kidneys of the lamb.' Research in Veterinary Science, 60:122-125.

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2:577–80.

Bartlett Z (2018) Apoptosis in embryonic development. The Embryo Project Encycopedia. https://embryo.asu.edu

Bignami G (1996) Economical test methods for developmental neurobehavioural toxicity.

Environmental Health Perspectives 104(S2) 285-298

Bradford Hill A. The Environment And Disease: Association Or Causation? In: Proceedings of the Royal Society of Medicine. Vol 58. Royal Society of Medicine Press; 1965:295-300.

Broussard C, Rasmussen SA, Reefhuis J et al (2011) Maternal treatment with opioid analgesics and risk for birth defects. Am.J.Obst.Gynecol. 204: 314 e1-11.

Changeux JP, Danchin A (1976). Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. Nature 264: 705–712.

Conradt E, Sheinkopf SJ, Lester BM, Tronick E, LaGasse LL, Shankaran S, et al. Prenatal substance exposure: neurobiologic organization at 1 month. J Pediatr 2013; 163: 989–94 e1.

Coyle MG, Salisbury AL, Lester BM, Jones HE, Lin H, GrafRohrmeister K, et al. Neonatal neurobehavior effects following buprenorphine versus methadone exposure. Addiction 2012; 107 (Suppl. 1): 63–73.

Creeley CE, Dikranian KT, Johnson SA, Farber NB, Olnesy JW (2013) Alcohol induced apoptosis of oligodendrocytes in the fetal macaque brain. Acta Neuropathologica Communications 1: 23

Cuervo R, Concepcio´n Valencia, Roshantha A. S. Chandraratna, and Luis Covarrubias. Programmed Cell Death Is Required for Palate Shelf Fusion and Is Regulated by Retinoic Acid. Developmental Biology 245, 145–156 (2002).

Desai RJ, Huybrechts KF, Hernandez-Diaz S, Mogun H, Patorno E, Kaltenbach K, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. BMJ 2015; 350: h2102.

Fodor A, Timar J, Zelena D. Behavioral effects of perinatal opioid exposure. Life Sci 2014; 104: 1–8.

Gee D. Establishing evidence for early action: the prevention of reproductive and developmental harm. Basic Clin Pharmacol Toxicol. 2008;102(2):257–266.

Gewolb IH, Fishman D, Qureshi MA, Vice FL. Coordination of suck-swallow-respiration in infants born to mothers with drug-abuse problems. Dev Med Child Neurol 2004; 46: 700–5.

Gilardi F, Marc Augsburger and Aurelien Thomas. Will Widespread Synthetic OpioidConsumption Induce Epigenetic Consequences in Future Generations? Front. Pharmacol. 2018, 9:702.. doi: 10.3389/fphar.2018.00702

Gill AC, Oei J, Lewis NL, Younan N, Kennedy I, Lui K. Strabismus in infants of opiate-dependent mothers. Acta Paediatr 2003; 92: 379–85.

Gutstein H B and Akil H (2006) Opioid Analgesics. Ch 26 In- Brunton LL, Lazo JS, Parker KL Goodman and Gilman's The pharmacological basis of Therapeutics. New York: McGraw Hill.

https://webbook.nist.gov/cgi/cbook/ Molecular structures and other characteristics of individual opioids: NIST Chemistry Web Book.

Harlan, R. E. & Song, D. D. Prenatal morphine treatment and the development of the striatum. Regul. Pept. 54, 117–118 (1994)

Hinchliffe S.A., Lynch M.R.J., Sargent P.H., Howard C.V., van Velzen D. (1992). 'The effect of human intrauterine growth retardation on the development of renal nephrons.' British Journal of Obstetrics and Gynaecology 99: 296-301.

Hu, S., Sheng, W. S., Lokensgard, J. R. & Peterson, P. K. Morphine induces apoptosis of human microglia and neurons. Neuropharmacology 42, 829–836 (2002)

Jacobsen MD, Weil M, Raff (1997) Programmed cell death in animal development. Cell 88 347-54

Kavlock RJ, Woodrow Seltzer R (1995) The road to embryologically based dose-response models. Environmental Health Perspectives. 104 S1 107-121

Kerr JF, Wyllie AH, Currie A R (1972) Apoptosis: A basic biological phenomenon with wide ranging implications in tissue kinetics. British Journal of Cancer. 26: 239-57

Kivisto K, Tupola S, Kivitie-Kallio S. Prenatally buprenorphine-exposed children: health to 3 years of age. Eur J Pediatr 2015. doi:10.1007/s00431-015-2562-0 [Epub ahead of print].

Liu AJW, Sithamparanathan S, Jones MP, et al Growth restriction in pregnancies of opioid-dependent mothers Archives of Disease in Childhood - Fetal and Neonatal Edition 2010;95:F258-F262.

Lu R, Liu X, Long H, Ma L. Effects of prenatal cocaine and heroin exposure on neuronal dendrite morphogenesis and spatial recognition memory in mice. Neurosci Lett 2012; 522: 128–33.

McCarthy M (2015) Opioids are commonly prescribed to women of reproductive age despite birth defect risk, US CDC study shows. BMJ 2015 350 h456

McGlone L, Mactier H. Infants of opioid-dependent mothers: neurodevelopment at six months. Early Hum Dev 2015;91:19–21.

Mazarakis ND, Edwards AD, Mehmet H (1997) Apoptosis in neural development and disease. Archives of diseases in childhood. 77 F165-F170

Mizuno N, Kokubu H, Sato M et al. (2005) G-Protein coupled receptor signalling through Gq and JNK negatively regulates neural progenitor cell migration. PNAS 102 (35) 12365-12370

Moe V. Foster-placed and adopted children exposed in utero to opiates and other substances: prediction and outcome at four and a half years. J Dev Behav Pediatr 2002; 23: 330–9.

Nassogne M-C, Evrard P, Courtoy PJ (1995) Selective neuronal toxicity of Cocaine in empryonic mouse brain co-cultures. PNAS 92 11029-11033

Oates JA (2006) The science of drug therapy. Ch 5 In- Brunton LL, Lazo JS, Parker KL Goodman and Gilman's The pharmacological basis of Therapeutics. New York: McGraw Hill.

O'Brien P (2006) Drug addiction and drug abuse. Ch 23 In- Brunton LL, Lazo JS, Parker KL Goodman and Gilman's The pharmacological basis of Therapeutics. New York: McGraw Hill.

Olney PD, Farber NB, Wozniak DF, Jevtovik-Todorovi V, Ikonomidou C (2000) Environmental agents that have the potential to trigger massive apoptopic neurodegeneration in the developing brain. Environmental Health Perspectives 108 S3 383-388

Patrick S, Dudley J, Martin PR, Harrel FE, Warren MD, Hartmann KE, Wesley Ely KE, Grijalva CG, Cooper WO (2015) Prescription opioid epidemic and infant outcomes. Pediatrics 135(5) 842-850

Reed MG, Howard CV & Staats de Yanes G (2010). One-Stop Stereology: the estimation of 3D
parameters using Isotropic Rulers. Journal of Microscopy, 239: 54-65.

Robinson SE. Effects of perinatal buprenorphine and methadone exposures on striatal cholinergic ontogeny. Neurotoxicol Teratol 2002; 24: 137–42.

Sadraie SH, Kaka GR, Sahraei H, Dashtnavard H, Bahadoran H, Mofid M, et al. Effects of maternal oral administration of morphine sulfate on developing rat fetal cerebrum: a morphometrical evaluation. Brain Res 2008; 1245: 36–40.

Stein C (2016) Opioid Receptors. Ann Rev.Med. 67: 433-51

Stephens CW (2011). The evolution of vertebrate opioid receptors. Front Biosci. 14:1247-1269

Svensson A-L, Bucht N, Hallberg M, Nyberg F (2008) Reversal of opiate induced apoptosis by human recombinant growth hormone in murine foetus primary hippocampal neuronal cell cultures. PNAS 105 (20) 7304-7308

Tau GZ and Peterson BS (2010). Normal Development of Brain Circuits. Neuropsychopharmacology Reviews 35: 147-168

Tempel A, Espinoza K. Morphine-induced downregulation of mu-opioid receptors and peptide synthesis in neonatal rat brain. Ann N Y Acad Sci 1992; 654: 529–30.

Vandenbroucke J, Broadbent A, Pearce N. Causality and causal inference in epidemiology - the need for a pluralistic approach. Int J Epidemiol. 2015:1-12.

Vestal-Laborde AA, Eschenroeder AC, Bigbee JW, Robinson SE, Sato-Bigbee C. The opioid system and brain development: effects of methadone on the oligodendrocyte lineage and the early stages of myelination. Dev Neurosci 2014; 36: 409–21.

Walhovd KB, Moe V, Slinning K, Due-Tonnessen P, Bjornerud A, Dale AM, et al. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. NeuroImage 2007; 36: 1331–44.

van den Hoffa M. J.B.,, Stefan M. van den Eijnde, Szabolcs Vira´gh, Antoon F.M. Moorman. Programmed cell death in the developing heart. Cardiovascular Research 45 (2000) 603–620

Welle-Strand GK, Skurtveit S, Jones HE, Waal H, Bakstad B, Bjarko L, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009. Drug Alcohol Depend 2013; 127: 200–6.

Wolff K, Perez Montenajo R (2014) Opioid Neonatal abstinence syndrome: Controversies and implication for practice. Current drug abuse reviews. 7 44-58

Yanai, J. et al. Functional changes after prenatal opiate exposure related to opiate receptors' regulated alterations in cholinergic innervation. Int. J. Neuropsychopharmacol. 6, 253–265 (2003)

Yazdy MM, Desai RJ and Brogly SB (2015) Prescription opioids in pregnancy and birth outcomes a review of the literature. J.Pediatric Genetics. 4 (2) 56-70

Yuan Q, Rubic M, Seah J, Rae C, Wright IM, Kaltenbach K, et al. Do maternal opioids reduce neonatal regional brain volumes? A pilot study J Perinatol 2014; 34: 909–13.

Zandi-Nejad K1, Luyckx VA, Brenner BM. Adult hypertension and kidney disease: the role of fetal programming Hypertension. 2006 Mar;47(3):502-8. Epub 2006 Jan 16.

EXHIBIT D

I, Gregory E. Skipper, M.D., declare and state as follows:

1. I am a medical doctor, currently licensed to practice medicine in the State of California.

2. My full qualifications are set forth on my CV which is attached to this affidavit as Exhibit 1. In summary, I am board certified by the American Board of Internal Medicine and Addiction Medicine. I am a Distinguished Fellow of the American Society of Addiction Medicine. I am the Medical Director at the Center for Professional Recovery: Professionals Treatment Program and Comprehensive Diagnostic Evaluation Programs in Malibu CA, a position I have held from 2011 to present. I am also concurrently the Medical Director for Professional Boundaries, Inc., a position I have held from 2000 to present. I have also been a Medical Review Officer in Toxicology Consulting since 2005.

3. In terms of my education, I obtained a B.S., Magna Cum Laude, from University of Alabama, in Tuscaloosa, AL, in 1971. Thereafter I obtained my Medical Degree and was part of the AOA Honorary Society from University of Alabama School of Medicine in Birmingham, AL, in 1974. From 1974-1975 I participated in a Residency in Physical Medicine and Rehabilitation at the Spain Rehabilitation Center in Birmingham, AL. From 1975-1978 I completed an Internship and Residency in Internal Medicine at the University of California, San Diego.

4. I am a member of numerous professional groups/societies, and I have authored extensive scholarly publications, articles and editorials, book chapters, audio and video

presentations, peer reviewed abstract presentations. I have spoken at national conferences with over 100 presentations on various topics related to Addiction Medicine.

5. I have been a consultant for numerous government agencies, including the FDA, the DEA, and the Center for Substance Abuse Treatment (CSAT). I was appointed to the National Advisory Council for the Substance Abuse and Mental Health Services Administration (SAMHSA) by the Secretary of HHS and served in that government position from 2001 to 2006. I have consulted extensively with criminal courts, evaluated patients that are incarcerated, and have testified in county, state and federal courts. I have testified in over 100 administrative hearings.

6. In addition to the above, I have extensive experience as a medical director of addiction treatment centers. My present duties include the direct management and supervision of other mental health professionals specifically as it relates to the overall assessment and care of addiction treatment from intake through discharge and discharge follow up.

7. Based on my background, training, and experience, as well as my skill as a practicing Internal and Addiction Medicine physician, I am readily familiar with, and understand the requirements of the standard of care for diagnosis and treatment of patients with opioid use disorders.

8. I have been compensated at a rate of $600 per hour for my work on this case.

9. In rendering my opinions, I have reviewed and relied upon the 3/2/2021 document entitled “Individual Purdue Pharma LP Claimant Claims Evaluation Criteria” (“Claims Criteria”) provided to me by counsel for the NASAHC, and the documents cited herein.

10. In connection with the litigation, I have been asked to review the “temporal relationship requirement” for payment found in the Claims Criteria, Section 7(a)(i)(A)(3), which is later incorporated into the “level awards” which follow.

This provision reads:

> The showing required for a Tier 1A Base Payment is a temporal relationship between use of a qualifying product and the onset of addiction, dependence or substance abuse within six months after use of a qualifying product. There is a presumption that proof of qualifying product usage under the methods above within six months before the onset of addiction, dependence or substance abuse (as set forth in the Claim Form) is sufficient.

11. My opinions are as follows: i) in the vast majority of cases, the "temporal relationship requirement" can only be met by rank speculation at best, and fraud at worst; ii) the six month "qualifying window" bears no relationship to the science of addiction; iii) the Base Payment (which does not require medical records but merely a statement by Claimants on a Claim Form) require Claimants to make an unqualified "self-diagnosis" of complex medical conditions based on undefined scientific terms "addiction," "dependence" and "substance abuse," and then speculate as to the date onset of these conditions, and iv) the Level Awards require a medical diagnosis of "Opioid Use Disorder" even though that medical diagnosis did not exist until 2013.

12. Further bases for my opinions are below.

13. The terms "addiction," "dependence" and "substance abuse" are medical terms and diagnoses undefined in the TDP.

14. The terms "addiction" and "dependence" and "substance abuse" are medical terms for conditions which a lay person (or claimant) is unqualified to diagnose.

15. Even among the medical community, the definitions and criteria for the diagnosis of these conditions have varied over the years by provider, medical organization and authority.

16. For instance, the most widely used text for the diagnosis of mental and behavioral disorders is the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) published by the

American Psychiatric Association (APA). The term "addiction" has not appeared within the text of the DSM since 1994 with the publication of the DSM-IV.[1]

17. Rather than refer to "addiction," the DSM-V, published in 2013, merged the former diagnoses of "substance abuse" and "substance dependence" into the category of "substance use disorders" (SUD) which is diagnosed based on the presence of 11 criteria.[2] The severity of an individual's SUD is qualified as *mild*, *moderate*, or *severe* based on how many of the 11 diagnostic criteria are met. Regarding "dependence," the APA eliminated the diagnosis altogether, noting the confusion between "dependence" and "addiction," noting the former can be a normal body response to a substance.[3] [4]

18. Like the DSM, the International Classification of Diseases (ICD), which the CDC refers to as "the cornerstone of classifying diseases, injuries, health encounters and inpatient procedures," has not used the term "addiction" to refer to substance use disorders since 1964.[5] [6] Rather than refer to "addiction," the 10th Revision of the ICD currently uses the term "dependence syndrome."[7]

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[1] Schneider, J. (2019) "What's In A Name? In This Case, That Which We Call Addiction Is Not Dependence." Practical Pain Management, Volume 19, Issue 5, pp 6-7

[2] Martin Guha, (2014), "Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (5th edition)", *Reference Reviews*, Vol. 28 No. 3, pp. 36-37; Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, et al. (August 2013). "DSM-5 criteria for substance use disorders: recommendations and rationale". *The American Journal of Psychiatry*. 170 (8): 834–51.

[3] https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM-5-Substance-Use-Disorder.pdf

[4] Presumably, as written, a Claimant can qualify for compensation for "physical dependence" to an opioid, even though "physical dependence" and resulting "withdrawal" are normal biological responses to use of opioids and not alone diagnostic of "substance abuse" or "addiction."

[5] https://www.who.int/substance_abuse/terminology/definition1/en/#:~:text=ICD%2D10%20Diagnostic%20criteria%20for%20research&text=A%20strong%20desire%20or%20sense%20of%20compulsion%20to%20take%20the%20substance%3B,-Impaired%20capacity%20to&text=Persistent%20substance%20use%20despite%20clear,nature%20and%20extent%20of%20harm.

[6] https://www.cdc.gov/nchs/icd/icd10cm_pcs_background.htm

[7] Seddon R. Savage, Definitions related to the medical use of opioids: Evolution towards universal agreement, Journal of Pain and Symptom Management, Volume 26, Issue 1, 2003, pp 655-667.

19. Noting the "the confusing panoply of terms and definitions," the American Medical Association's Council on Scientific Affairs Panel on Alcoholism and Drug Addiction created a task force in the early 1980s that attempted to reach consensus on addiction-related terminology.[8] A panel of 80 experts from more than 20 professional organizations developed and rated definitions of 50 terms related to substance abuse, including *addiction, addict, physical dependence, tolerance*, and *chemical dependency*. Savage, et al, observed that "although substantial agreement was achieved, these consensus definitions contained a curious blend of attributes that perpetuated, rather than clarified, the confusion."[9] The current Merck Manual likewise observes that "the terms "addiction," "abuse," and "dependence" have traditionally been used in regard to people with substance use disorders. However, those terms are all too loosely and variably defined to be very useful…."[10]

20. Not only does the Base Payment require claimants to make an unqualified "self-diagnosis."

of complex (and undefined) medical conditions, it requires the claimant to speculate as to a "start date" on which these conditions started. Even if one were to assume that "addiction" as used in the TDP meant "dependence syndrome" as used by the ICD-10, that would require the claimant to not only self-diagnose what the ICD-10 refers to as "a cluster of physiological, behavioral, and cognitive phenomena," but also reduce the presence of such "phenomena" to

[8] R.C. Rinaldi, E.M. Steindler, B.B. Wilford, *et al.*, Clarification and standardization of substance abuse terminology. JAMA, 259 (1988), pp. 555-557

[9] Seddon R. Savage, David E. Joranson, Edward C. Covington, Sidney H. Schnoll, Howard A. Heit, Aaron M. Gilson, Definitions related to the medical use of opioids: Evolution towards universal agreement,
Journal of Pain and Symptom Management,
Volume 26, Issue 1,
2003,
Pages 655-667,

[10] https://www.merckmanuals.com/home/mental-health-disorders/substance-related-disorders/substance-use-disorders?query=addiction

a particular date. Addiction science does not lend to itself to such specificity. In fact, ten of the DSM-V's eleven diagnostic criteria for "Opioid Use Disorder" (reproduced below) do not refer to discrete events or occurrences but to recurrences, trends, and/or progressions which render assigning a specific date to them impossible.[11]

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Exhibits tolerance.
11. Exhibits withdrawal.

21. The six-month temporal relationship requirement "between use of a qualifying product and the onset of addiction, dependence or substance abuse" is arbitrary, bears no relation to the science of addiction and is contrary to the state of the art medical practice for the diagnosis of OUD set forth in the DSM-V. If the purpose of the six-month temporal relationship requirement is to establish a cause and effect relationship between a claimant's use of a Purdue product and subsequent "substance abuse, dependence or addiction," it woefully fails.

[11] Although "withdrawal" could arguably relate to a discrete event, according to the DSM, "withdrawal" and "tolerance" are not to be considered evidence or criteria for opioid use disorder for persons taking opioids under appropriate medical supervision.

22. Generally speaking, "addiction" requires a) repeated exposures to a substance that triggers the reward center of the brain b) in a genetically susceptible individual c) with environmental or psychosocial risk factors.

23. It is impossible to know which of the repeated exposures was causative of the "cluster of physiological, behavioral, and cognitive phenomena" of addiction, and impossible to predict when the phenomena (or substance abuse) will occur in a given individual. I am unaware of any studies that even *attempt* to answer those questions anywhere in the universe of scientific literature. It would require rank speculation to predict whether phenomena (or substance abuse) will result within 6 months, 12 months, 24 months, or 48 months from a given exposure. In fact, in order to diagnose an OUD, the DSM-V requires the presence of two or more of its stated criteria over a period of 12 months.

24. The temporal relationship requirement also fails to establish cause and effect because it improperly ignores pivotal earlier exposures to opioids in favor of later exposures when both were equally causative of an OUD. "Addiction" simply cannot exist without both "priming" or initial exposures, and "reinforcing" or repeated exposures.

25. I believe the correct (and majority) view is that both priming and reinforcing exposures play equally important causative roles in any resulting addiction. For example, in an addiction-proned individual who was started on oxycodone for three months, switched to hydrocodone for the next 12 months, and did not meet the DSM-V criteria for moderate OUD until 15 months, *all* of the individual's exposures would be considered causative of the disorder. (The same would be true of an alcoholism-prone individual who began drinking vodka, switched to brandy and was drinking scotch by the time he met the criteria for alcohol use disorder).

26. I am also unaware of any literature that predicts when "substance abuse" may occur in susceptible individuals following a given exposure.

27. As stated above, the term "dependence" is undefined in the TDP and no longer appears in the DSM due in part to the loss of any consistent use or meaning.[12] Assuming "dependence" is read to mean "physical dependence," physical dependence alone does not denote a medical harm from opioids nor is it diagnostic of an OUD. Rather, physical dependence refers to the normal and expected physiological adaptation that occurs in the presence of medications which act on the central nervous system.[13] Physical dependence is known to occur within as little as 5 days of appropriate, medically supervised, round the clock use of narcotics for post-operative pain and is a medical condition which cannot be diagnosed by a lay person.

28. The TDP states that in order to qualify for a Level Award (above and beyond a Base Award), a Claimant must furnish an "Opioid Use Disorder" diagnosis. My two major concerns with this provision are that a) as this provision is written, in addition to furnishing an Opioid Use Disorder diagnosis, to qualify for a Level Award, the Claimant must still meet the scientifically fraught if not impossible temporal relationship requirement set forth for Base Awards, and b) "Opioid Use Disorder" is a medical term of art requiring specific criteria for a diagnosis that did not exist until the publication of the DSM-V in 2013.[14] Unless it is the intent of the bankruptcy to limit Level Awards to those diagnosed with

[12] O'Brien C. Addiction and dependence in DSM-V. *Addiction*. 2011;106(5):866-867.
[13] Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry*. 2013;170(8):834-851. doi:10.1176/appi.ajp.2013.12060782
[14] PubMed lists 3,315 articles containing the phrase "opioid use disorder." Of these, 3,289 were published in or after 2013.

OUD by their treaters in or after 2013, this provision would require claimants to seek a retrospective diagnosis made solely for the purpose of qualifying for payment under the TDP.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this 21st day of April, 2021 at Los Angeles, California.

Gregory E. Skipper, M.D.
Distinguished Fellow,
American Society of Addiction Medicine
Declarant